ANNUAL REVIEW OF PHYSIOLOGY

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PREFACE

To people everywhere it is heartening to see signs of the war's approaching end. To scholars it should mean a renaissance of learning, a reconquest of opportunities for that intercourse of the minds without which it is folly to expect any sort of international amity and accord.

The Annual Review of Physiology has grown up in a bellicose world. Its friends, perforce, have had to be its more immediate neighbors. With the peace will come, we trust, an early restoration of the friendships of earlier years. We look forward with increasing eagerness to the full return of international collaboration in authorship. Science recognizes not the boundaries imposed by the political state. Its limits are set only by the receding barrier between the unknown and the known. A Review that sets out to present a critical appraisal of recent contributions to the literature of a given science speedily becomes aware of its own inadequacies if its boundaries are restricted by choice or by necessity to the work of only a few countries. In war the boundaries are fixed by the necessities or expediences of the moment.

In addition to the urgent need of international collaboration in authorship we continue to be acutely aware of the continuing difficulties in publication and in access to foreign periodicals. A large segment of fundamental work in the sciences may not yet be published. Many periodicals that reach us from abroad do so belatedly, some not at all. These difficulties, though far from minor, are but transitory: they should disappear promptly with the cessation of hostilities.

In view of all of this we cannot but be impressed by the great volume of literature, fairly readily available, that calls so insistently for review. The present volume of the Review, the largest we have yet published, bears silent testimony to this fact. Its preparation for the press has not been easy, and to our colleagues in authorship, to our editorial assistants, and to our printers we are greatly indebted for their fine cooperation throughout. To the writers of the individual reviews we feel especially grateful. Without exception they have been heavily burdened with other obliga-

tions and their willingness to accept this labor of love is the thing that makes the publication possible.

In answer to occasional inquiries it may not be amiss to mention that the *Annual Review of Physiology* is published jointly as a non-profit venture by the American Physiological Society and Annual Reviews. Reimbursement for services rendered is received by the editorial and business staff: directors and members of the editorial committee serve without compensation. The modest surpluses that are earned in the better years constitute a necessary reserve against operations in the lean years.

It has been a source of regret that the reviews by C. B. Davenport on "Growth," M. G. Larrabee on "Visceral Functions of the Nervous System," and A. P. Richardson on "Chemotherapy," previously announced for publication in the present volume, could not be completed in time and had to be omitted.

A.J.C. J.M.L.
J.F.F. F.C.M.
V.E.H. W.J.M.
M.H.J.

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ERRATA

Volume VI, page 51, line 18: *for* Vitamin B_1 deficiency, *read* Vitamin B_6 deficiency.

page 406, line 21: *for* It is fortunate, *read* It is unfortunate.

PERMEABILITY

By S. C. Brooks

Department of Zoology, University of California, Berkeley, California

Three years have elapsed since this topic was reviewed here by Blinks (1). The present review covers the period from mid-1941 to mid-1944. Delays in the reception of foreign literature have necessitated occasional reference to earlier publications. Permeability is understood to contribute to an understanding of passage of permeants through the plasma membrane or several such in epithelia. The reader is referred to reviews on absorption or secretion by special tissue systems (digestive system, liver, pancreas, kidney, skin, placenta, plant roots, and storage tissues, etc.), in this or previous volumes as well as in the *Annual Review of Biochemistry*.

Permeability of natural membranes has been treated in the book by Davson & Danielli (2). It adopts Danielli's (3) concept, in which diffusing molecules surmount potential energy barriers in moving from one to the next resting region and must attain enough kinetic energy to do this, and to add to their potential energy or lose it in moving from one phase to another. This leads to the use of the temperature coefficients in relation to permeation. Methods, criteria here developed, experimental data, plasma membrane structure, and theories of permeability are treated. The review by Alvik (4) covers a range of related topics such as respiration, transport, action of stimuli, etc., as well as permeability itself.

Driving forces.—Diffusion is generally recognized as the most fundamental and important driving force causing permeation. A paper by Vinograd & McBain (5) treats the diffusion of electrolytes and of the ions in their mixtures. When there is diffusion of water through membranes it may flow in sufficiently large columns to form a phase in relation to which solutes themselves diffuse, both presumably because of activity gradients. This is termed a "drag effect." Such a possibility is mentioned by Landahl (6) and Wildbrandt. (7). Linderstrøm-Lang (8) gives a mathematical treatment of the diffusion of solutes in a three-chamber model.

Formulations.—The use of mathematics in describing or predicting the course of permeation has called out several papers,

which however will be mentioned with the aspect of permeability as they occur. A study by Kostitzin (9) is of a general nature, as is also that of Morales & Shock (10) who discuss solvent and water transfer and membrane potentials in the chloride shift in erythrocytes.

Macovski (11) has formulated equations, using the method of least squares, applicable to estimation of poisoning "constants" of substances acting on living cells.

Artificial membranes.—Macovski & Stan (12) imitate living gills by using cellophane tubes packed with glass beads to give channels of the size of capillaries, and measuring the rate of penetration of oxalic acid through the membrane. This confirms the validity of Macovski's "poisoning equations." In later publications (13, 14) these authors amend and test with oxalic acid and potassium chloride the poisoning equation, giving a new form.

Cellulose ester membranes vary in their permeability to water with the type of esterifying groups (15). Nitro- and acetyl cellulose membranes are the most permeable and their permeability increases with the increase in nitro or acetyl content. Ethyl cellulose membranes are like membranes with small acetyl content. Benzyl and rubber containing membranes are less permeable to water.

The work of Sollner and his co-workers concerns "oxidized" cellulose membranes; i.e., which have an increased number of carboxyl groups. Sollner, Abrams & Carr (16) treat the occurrence of polar groups found in commercial collodion membranes, and the same authors (17) show that collodion membranes, gently oxidized, as by sodium hypobromite, display increased concentration potential differences. They are considered to owe their behavior to their micellar, in contrast to a homogeneous structure (18). These potentials are not regularly correlated with the titrable base exchange capacity of dried collodion membranes (19), and thin membranes show the maximum value with no further rise with increasing thickness of the order of ten microns (20). Sollner & Anderman (21) find that there is great variation among different collodions in the proportion of carboxyl groups which are neutralized by 0.01 *N* potassium hydroxide, namely these variations are largely due to differing structure and amount to from 1/770 to 1/13. The more active preparations neutralize more alkali.

Carr & Sollner (22) conclude that uptake of water by collodion membranes involves binding of water, since the gain of volume of

the membrane is only about 60 to 70 per cent of the gain of weight. In solutions of strong electrolytes no further gain in weight occurs. Solutes may be differentiated according to their hydrophile or carbophile affinity (23). The former (e.g., glycerol, glucose, citric acid, etc.) affect the swelling of the collodion membrane as the strong electrolytes do, that is exert only osmotic forces; the carbophile solutes (butyl alcohol, butyric acid, valeramide, phenol, etc.) markedly increase this swelling, and are "accumulated" in the membrane by their binding by carboxyl groups. The authors refer to the finding by many earlier workers of the property of these solutes in increasing the peremability of the collodion membranes, which they visualize as an opening up of the membrane structure. Abrams & Sollner (24) coat these membranes with protamines, producing long-lasting potential differences which show the transformation of negative to positive membranes.

The properties of dried collodion membranes are distinctive. Cellophane differs, for example, by not selectively hindering the permeation of anions, as collodion does (25). Copper ferrocyanide cellophane membranes are permeable to urea, but not to glucose (26). This may be due to the carbophile or hydrophile nature of the permeants or to differences in size of molecules. Both correlations are permissible (23). The role of adsorption of anions on copper ferrocyanide deposited in filter paper or on parchment was studied by Willis (27). The variation with concentration of the potential differences between two solutions of different concentrations is interpreted as a result of the ionic atmosphere in the pores of the membranes. Higher concentration, or polyvalent cations thin the ionic atmosphere in the pores so that anions can penetrate more freely, and reduce the potential of the more dilute solution. Polyvalent anions oppose this. This resembles qualitatively their influence on the collodion membrane, which also displays selective hindrance to anion permeation. Fletcher (28) examined the agreement between the postulates for various plastic membranes and the data obtained by Meyer & Sievers (29). The latter postulate that "selective effects" rule the concentrations of ions bound within the membrane, and that "sieve effects" affect the retardation of one or more of ions passing through the membrane. Fletcher finds lack of satisfying correlation between postulates and data.

Osterhout (30) has reported potential differences between two different salt solutions separated by a layer of nitrobenzene. In

this model, ions are seriated in the order from negative to positive: $Rb > K > NH_4 > Na > Li$. Guaiacol lessens the potential difference between potassium and sodium salt solutions. This imitates effects found in experiments with *Nitella flexilis*.

Goldman (31) studied the conductance, rectification, and capacitance, using small direct or alternating currents (35 to 100 kc.), and potential differences when diverse solutions are used with lipoid-impregnated collodion membranes. Their values under various conditions were calculated, assuming that the membranes were micellar, with selective diffusion of hydrogen, potassium, and lithium ions through it, and found to agree well for most of these properties, but only qualitatively for conductance. There was general agreement with biological materials. This appears to lead to a fuller understanding of these and living membranes (32).

Macovski & Zinca (33) failed to find a facilitation of the passage of amyl alcohol, due to its own surface activity, through a cellophane membrane. Other investigators had found the surface active saponin to facilitate the passage of hemoglobin through a collodion membrane.

Chemical and physical structure of living membranes.—Dziemian (34) determined the changes in the amounts of lipoids in rabbit erythrocytes following extensive destruction of erythrocytes by phenylhydrazine, and sought correlation between these changes and the prominent changes in permeability to solutes of the remaining population. There was great increase in phospholipid per sq. mm. in some cases, but in no case was correlation found.

The structural importance and arrangement of lipoids in catfish nerve sheaths were found to be as previously described for other forms (35), but Wolpers (36), using an electron optical microscope, concludes that erythrocytes have plasma membranes which consist of a skeleton of long protein micelles in whose interstices lipoids occur at random, rather than as in the previously surmised bimolecular layers; no mosaic structure was visible. Here control of permeability is attributed to the lipoids. Wrinch's concept of the plasma membrane depends on the validity of the cyclol hypothesis of protein structure, the plasma membrane being conceived to consist of linked cyclol proteins (37). Because of wide lack of acceptance of the cyclol concept, plus the fact that contemporary studies are opposed to this, it seems that Wrinch's suggestion retains little usefulness.

Factors, other than ions, affecting the permeability of plasma membranes.—Surface active substances have been found to increase the permeability of plasma membranes. Ikemune (38) finds this to be true for ethyl alcohol.

Höber & Höber (39) observed coloration with trypan blue or soluble blue of the Kupffer cells in perfused frog livers. When perfused with Ringer solution there was little or no coloration; with serum there was increased diffuse coloration of the cytoplasm, but not of the nucleus, of the Kupffer cells. These differences were attributed to surface-active serum constituents. The addition of nonpolar-polar surface active agents (bile salts, alkyl sulfonates, hexyl esters) increased staining together with swelling and syncytium formation, or in higher concentrations led to nuclear staining and finally to complete cytolysis. The authors felt that the smaller effects belong in the realm of physiological changes, and regard the agents as typical cytolytic materials. Sugars and polycyclic or organic acids inhibit the secretion of dyes into the bile, and sucrose and sodium succinate greatly decrease the staining of Kupffer cells. In considering the molecular picture, the authors point out the alteration of fields on the surface of lipoid phases of the plasma membrane, in which the nonpolar moiety of the detergents finds lodgement. There is also the well-known property of these detergents of unfolding or disrupting single and conjugated proteins. These seem to be present in the plasma membrane. It may well be that both actions are important in determining the permeability of the plasma membranes.

Saponin is reported by Hoffman (40) to increase the permeation of calcium through the intestinal mucosa. The effects of narcotics and analeptics on the permeability of frog skin to ions has been described by Hoffman (41). In low concentrations ethyl urethane, paraldehyde, amylene or chloral hydrate, barbital, and phenylbarbital in subnarcotic concentrations increase reversibly the permeability; in narcotic concentrations they decrease it, only at first reversibly. The analeptics metrazole, strychnine, coramine, and picrotoxin antagonize these.

Irradiation, either roentgen (42, 43) or ultraviolet (44), promotes ion penetration into erythrocytes. From the amounts of energy requisite Liechti, Wilbrandt, and their co-workers conclude that constituents other than the nucleoproteins of the nucleus are responsible for these results. It appears that the proteins are de-

natured by irradiation, but other constituents are not excluded.

The permeation of erythrocytes by potassium was reported by Tukuda (45) to be increased by exposure of acidotic rabbits to negative ions of air, while positive ions had no effect.

Hemolysis.—This phenomenon, like those of the preceding section, depends upon the alteration of the plasma membrane. Wilbrandt (46) distinguishes between hemolysis due to osmotic pressure differences only, and a type of hemolysis, the "colloid osmotic hemolysis," which he attributes to the loss of the impermeability to cations by erythrocytes, and the ensuing penetration of salts and water up to and beyond the critical hemolytic level. It is not easy to envision the requisite driving forces for salts and water where the erythrocytes are normally in osmotic equilibrium with the medium. Colloid osmotic hemolysis is said to be shown when beef erythrocytes are hemolyzed by ethyl alcohol, acetone, chloroform, x-rays, saponin, bacteria, or bee venom, or when sterile cells hemolyze spontaneously. Freeman *et al.* (47) produced hemolysis *in vivo* in dogs by injecting 5 mg. per kg. of soaps or fatty acids.

Ponder (48) considers that such substances as serum, hemoglobin, or glucose react with constituents of the erythrocyte plasma membrane in small regions, and that the reaction products have a different resistance to hemolysis. The nature of the reaction is not given. Hemolysis is thought of as starting at the "weakest" spots, which may be arranged in regular spatial patterns, and spreads from them.

The capacity of the strongly bound cupric and mercuric ions to increase the hydrogen ion concentration at the erythrocyte plasma membrane (during penetration only) is thought by Wilbrandt (49) to accelerate thereby the hemolysis of these cells by glycerol. This is, therefore, a pH effect secondary to the action of these toxic ions, and involves no permanent alteration of the plasma membrane. Davson (50) considers the hemolytic effect of potassium salts to be due to osmotic swelling. This swelling results from different rates of loss of sodium (possibly its ions) and gain of potassium, and the nature of the anion is an important decisive factor. The fact that the anions (sulfocyanide, nitrate, bromide, chloride, and acetate) affect the permeability to potassium and sodium in opposite directions raises many questions. Davson claims that recourse to the familiar Hofmeister hydration and swelling rule is finally shown to be futile.

The reversibility of the changes brought about by osmotic hemolysis has been demonstrated by Hunter, Stringer & Sterling (51) who show, that on the reversal of hemolysis, the shadows retain their relative permeabilities for both lipoid-insoluble molecules (glycerol, malonamide) and lipoid-soluble molecules (monacetin) in spite of their generally enhanced permeability.

Permeability to Molecules

Gases.—Kiese (52) gives a theoretical discussion of the absorption of gases from the pleural cavity, assuming that only the pressure gradient and not any active absorption process, determines the movement of gases through the pleura. Similarly Wu (53) and Bloch (54) formulated equations governing the movement of gases such as oxygen or krypton from the blood into the tissues. Smith & Morales (55), adding to the participating factors considered, set up equations based on a number of factors, including permeability. The equations are tested by the observed movement of krypton.

Water.—There has been much discussion of osmosis and related terminology. Edlefsen (56) uses the free energy changes of water in plants and soil as the fundamental property. Discussion by twenty-seven biologists and a résumé by Edlefsen is appended. Considerable difference between the viewpoints is represented. Crafts (57) favors the concepts of many contemporary plant physiologists (diffusion pressure deficit, turgor pressure, and osmotic pressure) and here discusses comments on his preliminary presentation, issued for discussion. Crafts fears practical difficulties in teaching the physicochemical approach. Eyster (58) surveys usages and preferences. He advocates the use of the term "osmosis" for the diffusion of water or solute through a membrane, and proposes a new term "osmotic pressure deficit" to replace such terms as "suction force" or "diffusion pressure deficit." Much can be said for this usage.

The so-called "nonosmotic force" is a hypothetical force which appears to manifest itself in discrepancies between the osmotic pressure of cell contents in plant tissues measured by the depression of the freezing point of expressed juices, and that measured by the known osmotic pressure of a solution just able to plasmolyze the cells (59, 60) or to stop water intake by roots (61). It seems possible that this concept is based on irregularities in the freezing point of colloid-containing solutions. These merit attention. On

the experimental side there are papers by several: Eaton (62) studied exudation from the cut-off stems of several plants and from tomato hydathodes. Measurements of osmotic pressure and chloride concentrations in the sap of roots, xylem, and leaf were made. No evidence of the existence of any nonosmotic force was detected in any of these cases. The papers of Long (63) who measured water intake by tomato roots, of Hayward & Spurr (64), studying water intake by corn plants, and of Blum (65) who found a constant osmotic pressure difference between leaf and surrounding watery solution for mangrove plants, which grow in fresh, brackish, and sea water, all emphasize the role of osmotic pressure as the only driving force for plant water intake. Gasser (66) raised plants of seventy-five species with excess and deficit of water, and found that the "suction force" (osmotic pressure deficit) of leaf or flower epidermal cells is not characteristically constant. Beck (67) and Bujard (68) show that actively growing cells, or those in a premitotic state, have osmotic pressures higher than other cells of the plants studied. Commoner, Fogel & Muller report stoppage of water loss or water intake by discs of potato tubers in hypertonic solutions of sucrose exposed to auxin in suitable concentrations (69). Since auxin changes the amount and nature of the reaction products, the water movements seem to be due to shifts of the equilibrium and, therefore, of the driving force, and not to any change in permeability itself. Parts of cells may show response to osmotic pressure: the "cap" of plant cells plasmolyzed in potassium chloride (70) and pigment granules of sea urchin (*Arbacia punctulata*) eggs (71).

Roepke & Baldes (72) have studied the nature of the "nonsolvent volume" in erythrocytes. They determine osmotic pressure by balancing the temperature changes shown by thermal couples on whose surfaces drops of fluid cell material and salt solution were laid. When two fluids give the same cooling effect, due to their evaporation rate, they are considered to have the same osmotic pressure, a colligative property shown by an equilibrium. This assumption is defended for this case. This test, together with mixture of cell content with suitable solutions, confirms that the "nonsolvent volume" is not constant for one lot of erythrocytes. They attribute this deviation to the presence of bound water, part of which is capable of dissolving solutes, plus dissociation of hemoglobin. However, this deviation with varying swelling or shrinkage

of erythrocytes is thought by Ponder (73) to be due to the water content of hemoglobin, especially in the form of "wet" crystals, and their elastic rigidity. Hypertonic solutions often appear to produce crenation and hemoglobin crystallization, and may also display rigidity. This rigidity, in addition to the binding of about 5 per cent of the erythrocytes' water, is adequate to account for the anomalous osmotic behavior of the erythrocytes.

The loss of previously acquired penetrating substances by erythrocytes leads to swelling, the driving force for water increasing with the loss of the penetrating substance. Wilbrandt (7) formulates equations, giving the rate of water movement, using the progressively changing driving force, and also equations for the movement of the permeant. He feels that this loss is modified by the stream of the entering water (6, 8). Shapiro (74) reports that water enters the egg of a marine worm, *Chaetopterus pergamentaceus*, at a rate of 0.49 and 0.61 cu. μ per sq. μ per min. per atmosphere for unfertilized and fertilized eggs respectively. The nonsolvent volumes are given as 38.8 and 29.9 per cent of the whole volumes of unfertilized and of fertilized eggs. Similar differences as a result of fertilization are familiar. Lucké & Ricca (75) describe the volume changes of the egg of the oyster (*Ostraea virginica*) at various osmotic pressures in diluted sea water. This requires reciprocity between osmotic pressure and cell volume, provided that a nonsolvent volume of 44 per cent is deducted from the total volume of the egg. Water permeates inwards or outwards with a permeability constant of 0.6 cu.μ per sq. μ per min. per atmosphere.

The vitelline membrane of the hen's egg was reported by Orrú (76) to act as a semipermeable membrane in allowing water to penetrate from fresh water into the yolk in amounts proportional to its age.

When heavy water was injected intravenously (as isotonic sodium chloride solution) into a guinea pig it was completely distributed in all tissues in less than six minutes, and Flexner *et al.* (77) calculated that 73 per cent of the heavy water was exchanged through the vessel walls in one minute.

Kinsey, Grant & Cogan injected saline-containing heavy water into the peritoneal cavity of the rabbit, and determined its rate of appearance in the blood and aqueous humor (78). They ascertained how fast it passes into the aqueous humor and deduce a flow of water of 50 cu. mm. per minute. A flow of 13 cu. mm. per minute

was found in the monkey. Instead of flow or ultrafiltration, this seems to be a case of distribution of heavy water, presumably accompanied by movement in the opposite direction of ordinary water. This would mean that the actual flow of water, both types, would be greatly less than the figures given. The same reasoning is applicable to the similar movement of radioactive ions, reported in the same paper, and the disappearance of heavy water from the aqueous humor. Nevertheless, the figures given on these and other water movements are qualitatively significant. In a later paper Cogan & Kinsey (79) studied the flow of water through the cornea with its overlying membranes (epithelium, endothelium, and Descamet's) in response to an osmotic gradient. This occurs in the direction of posterior to anterior, but the damage produced by the osmotic pressure prevented the movement in the opposite direction. The former was at the rate of about 4 cu. mm. per sq. cm. per minute. The epithelium was the most important. The same authors (80) measured the flow of water through the cornea under a hydrostatic pressure from 5 to 410 mm. Hg. The flow was roughly parallel to the pressure, the ratio varying as 1 to about 1.7. The same three papers deal also with solute movement, which is considered below.

Nonelectrolytes.—Studies were made by Skene (81) of the rate of passage of glycerol, glucose, and sucrose and a salt through the cell walls of the beet root in the absence of the protoplast. His results expressed as diffusion constants, were compared with similar values for cells with protoplasts for ten species quoted from the literature. The protoplast greatly retarded the movement of the permeants, so that the ratio of the resistance of the wall plus the protoplasm to the resistance without the protoplast were 0.15 to 0.7 for glycerol, 5 to 8 for glucose, and 5 to 8 for sucrose, all multiplied by 10^4. However, the cell wall exhibits considerable resistance to permeation. Kreuz (82) studied the relative permeability of living cells from various tissues of several species of plants to urea and glycerol; for stamen hair cells of *Tradescantia elongata*, the permeability to urea about equals that to glycerol; the ratio for epidermal cells of *Allium cepa* was 6; *Valeriana officinalis*, 21; *Caltha palustris*, 55; and *Mentha aquatica*, 130; while extremely high ratios were found for cells of *Campanula trachelium* and basal foliar cells of *Taraxacum*. Calcium chloride and glucose retard this permeation more strongly as the ratio rises, and with the effect of

calcium chloride tending to exceed that of glucose where permeability to urea is very high, as in the last two species mentioned. The author feels that these data show that both pore and lipoid solubility are important, but that permeation through the pores greatly exceeds the solution permeability. Höfler (83) points out that diatoms are freely permeable to sugars.

Musfeld (84) suspended bakers yeast (*Saccharomyces cerevisiae*) in 0.5 % glucose buffered with 0.067 *M* KH_2PO_4, and measured the glucose taken in, oxygen used, and carbon dioxide produced. The amount of glucose used was calculated on the assumption that one mole of glucose produces six moles of carbon dioxide. Table I shows that the glucose taken in is 5.4 to 8.8 times that metabolized.

TABLE 1

INTAKE AND USE OF GLUCOSE BY YEAST*

Concentration of suspension %	Temperature °C	Glucose intake †	Oxygen used †	Carbon dioxide produced †	Glucose used (calculated) †
0.2	25	10.7	0.6	1.22	12.2
0.2	35	14.2	0.63	1.85	19.2
0.6	25	5.9	0.60	1.01	9.1
0.6	35	9.8	0.69	1.53	17.3

* From Musfeld (84).

† The values represent gm. $\times 10^9$ per sq. cm. per sec.

The remainder appears at least in part as glycogen. It was noted that the presence of glucose was essential for the respiration measured. Lucké & Ricca found the permeability of the egg of the oyster to diethylglycol and glycerol to be 27.2 and 20.7×10^{-15} moles per sq. μ per min. per mole per liter respectively (75). Orskov (85) calculated permeability constants of human erythrocytes on the simplifying assumption that the Fick diffusion laws hold true. Their mean values were: glycerol, 1.64; glucose, 0.099; thiourea, 0.392; malonamide, 0.0527; hexamethylene tetramine, 0.312; and ammonium acetate, 0.449, the end point being the time required for the permeant to penetrate into the erythrocyte to a level one quarter of that in the suspending fluid.

Urea appears to be present in the water of the human erythrocyte in excess of the amount in the water of the plasma, even after

allowances are made for the bound water in both phases. The post-absorptive mean ratio is 1.14; after a meal the ratio approaches one. In discussing these data, Ralls & Crohn (86) suggest the possibility that urea may react with hemoglobin; the necessary amounts of hemoglobin and excess urea are compatible with those found.

Moore, Scheie & Adler (87) studied the concentration of urea in the aqueous humor of the eye. This is normally lower than that in the blood stream, and responds slowly to the rise of urea injected into the blood. The concentration in the aqueous humor reaches equilibrium, i.e., steady values, only after seven hours. Water passes from the blood capillaries, through the aqueous humor and flows off in Schlemm's canal, and permeates the capillary walls faster than urea does. Kinsey & Grant (88, 89) have investigated the rate of accumulation of urea and levulose (fructose) and six salt ions in the aqueous humor. The concentrations in the plasma were followed by ultrafiltration and selective diffusion, and a continuous record made of the concentrations of the solutes in the plasma and aqueous humor. Duke-Elder & Davson (90) criticize the concepts of Kinsey & Grant (89), apparently not understanding the unfortunate use of "ultrafiltration" and "differential dialysis" by the latter. The difficulty evaporates when it is realized that both groups are discussing selective permeability.

The sugars penetrate from the blood into the aqueous humor of the dog's eye at rates dictated by their molecular size, xylose, glucose, and raffinose having been tested, the latter barely penetrating through the capillary walls and pigmented epithelium (91). Inulin penetrates only if vasodilating drugs are used. The normal level of glucose in the aqueous humor is about 3.5 per cent lower than in the blood plasma.

Macovsky & Stancu (92) consider the toxic action of saponin on the fish, *Alburnus lucidus*, which is manifested by struggling attributed to impaired oxygen supply. The previously developed poisoning equations of this author (11, 14) proving inadequate are here modified.

Permeability to Weak Electrolytes

The distribution of electrolytes between muscle and intercellular fluid has been investigated extensively. The recent work of Boyle & Conway (93) postulates that the distribution of permeating ions depends on a Gibbs-Donnan equilibrium. This appears to account for many of the observed ion concentrations.

However, a direct determination of the bicarbonate ion content of muscles is greatly needed. In this connection it must be emphasized that molecules and ions are not alternatively permeant or non-permeant; but there are all degrees of penetrabilities. Undoubtedly the bicarbonate ion has a much lower penetrability than carbon dioxide. Wallace & Hastings (94) endeavor to determine whether the bicarbonate ion penetrates muscle fiber membrane or not, and favor the latter.

Bouillenne (95) measured the rate of recovery from plasmolysis of onion bulb epidermis cells, previously plasmolyzed in 0.66 *M* KCl when transferred to 0.66 *M* ammonium formate, acetate, butyrate, or valerate. Maintaining a pH of 7.0 in the bathing fluid, Bouillenne found that the rate of penetration, as shown by recovery from plasmolysis, increases with increase in the number of carbon atoms in the acid radical. From the work of Jacobs (96) it may be assumed that membrane hydrolysis is going on, and the acids themselves are the permeating form. The seriation in the order of "lipoid solubility" emphasizes the importance of this characteristic in determining the penetrability of molecules.

The penetration of penicillin from the external eye surface into the aqueous humor is best accomplished by iontophoresis. Without this, penicillin penetrates only one-tenth as fast, but aerosol doubles this rate (97).

Dyes.—Although some dyes are so strongly dissociated as to be counted as strong electrolytes, the majority of dyes are weak electrolytes so that this group may be considered here. The most conspicuous study of the period here considered is that of Drawert (98), who tested the permeation of sixty dyes into living cells of the white petals of *Chrysanthemum leucanthemum*, *Philadelphus*, etc. Of these dyes, about three-fifths with the smaller molecules, enter the cells, while the larger molecules are unable to permeate, or do so only slowly. To this extent, this finding supports the ultrafilter concept of the plasma membrane, but it is also noted that the dyes soluble in neutral chloroform are rapidly taken in and stain the cytoplasm diffusely, while the chloroform insoluble dyes are able to permeate the cells only very slowly, stain the vacuoles, and are more firmly fixed than the other group. Drawert contrasts the chloroform soluble dyes of the first group which form solutions in the cytoplasm of the cells and penetrate passively, with dyes of the second group which he considers to permeate only by virtue of the aid of short-lived intermediary substances (possibly of metabolic

origin). The first group is toxic. These generalizations lead Drawert to deny the participation of "lymphoid activity," that is, the direct use of the energy of respiration. The denial seems to be only a definition of the term "lymphoid activity," since there may well be a question as to the way respiration supports lymphoid activity. Here, as so often, more knowledge of the molecular architecture of the cytoplasm and plasma membrane is urgently needed. Schöpfer (99) continued his investigation of thiochrome, a substance closely related to aneurin (thiamine), and detected by its fluorescence. Many plants were used, notably seedlings of *Impatiens parviflora*, *Trapa natans*, and *Iresine* spp., and in general thiochrome was found in the pith, cortex, and endoderm of roots, and in other tissues less often. Lactoflavin (riboflavin) was also found to be absorbed by plant tissues. Gilbert & Blum (100) studied closely the intake of rose bengal by rabbit erythrocytes. These were suspended in an istonic solution of sodium phosphate of pH 6.7, and the dye was added in concentrations of 10^{-5} to 10^{-6} M. Although dye intake persisted slowly thereafter, the equilibrium concentrations were assumed to be those found after six hours. The amount of dye taken in was proportional to its initial concentration in the menstruum. The time curve of intake was not expressible by any of the three hypotheses considered: (*a*) that the dye was partitioned between two immiscible solvents; (*b*) the dye was absorbed; or (*c*) the dye reacts with a cell constituent, a bimolecular reaction. These were considered in detail, and the authors feel that the dye is partitioned between three or more immiscible solvents, plus one or more reactions. No fully satisfactory conclusion was reached.

The work of Höber & Höber on the effects of detergents, sugars, and organic acids on the permeation of dyes mentioned above (39), is interesting here in that there is a definite difference of permeability of secreting and Kuppfer cells to trypan blue, and in the fact that dyes are secreted by the liver cells into the bile, the ratio of the concentrations of bile to blood reaching several hundred or a thousand. The excellent reviews of Höber (101) and Visscher (102) on dye secretion are mentioned in connection with the secretory process.

Permeability to Ions

Richards (103) reviews mineral nutrition of plants through 1943, and animal mineral nutrition was reviewed through 1942 by Maynard & Looski (104). See also McCance & Widdowson (105),

for an additional review. Householder & Williamson (106) consider mathematically the diffusion of electrolytes and the electrical forces resulting from differences in the mobilities of ions. Mathematical formulation of the movement of bicarbonate ions entering and leaving the blood following exercise is given by Morales & Shock (108) using data obtained by Shock (107). Almasy gives a mathematical discussion of the distribution of ions between living cells and the medium (109).

Adsorption of ions.—The uptake of ions by bacteria often presents an adsorption picture rather than permeation. McCalla & Foltz (110) in the case of *Escherichia coli* find that these cells will take up hydrogen, and less accurately magnesium or methylene blue ions obeying the adsorption isotherm $x/m = kc^{1/n}$ and reaching an adsorption capacity consistent with the estimated number of adsorption points present. Hoffman (111) immersed a fresh water alga in a uranyl salt containing $10^{-6}\mu$g. of uranium and found that these cells took up enough of the uranium salt to give 9.1×10^{-4} per cent of uranium. It is almost sure that uranyl ions displaced other ions at adsorption points or polar groups, particularly in view of the high valency of this ion. It seems probable that the thyroid gland contains material which is specifically fitted to combine or react with iodine and to some extent bromide (112, 113, 114). It may be that a similar mechanism operates in the adsorption of selenium (115) but metabolism complicates the situation. The loss of salts from potato tubers irradiated with ultraviolet light reported by Lepeschkin (116), and attributed to "vitaids," may reflect a change in such adsorption.

Absorption of ions.—Osterhout (117) points out that the protoplasm of *Nitella* and *Valonia* and other algae swells because of intake through the plasma membrane of a salt, presumably sodium chloride, followed by equilibration of its osmotic pressure with that of the vacuole by robbing the latter of water. This assumes lower permeability of the vacuolar membrane to salts, a feature supported by Osterhout's electromotive observations, as well as by some earlier work (118). While the semipermeable nature of the surface membranes is established for all except possibly the smallest cells, the role and nature of adsorption points or equivalent attractive forces within the cell is still not well clarified. From the experience of soil chemists one is prone to attribute to steric factors together with such attractive forces the difference in penetrability of closely related ions.

Lasnitzki & Brewer (119) continue their earlier work to show that while normal tissues do not greatly alter the ratio K^{39}/K^{41} as they penetrate, rapidly growing carcinomata contain an excess of K^{39} while the hematopoietic tissues, which continually export rapidly growing cells, display an excess of K^{41}. Apparently the smaller ion, K^{39}, enters the living cells faster than K^{41}, and hence must precede it in rapidly growing cells. Jacques records a similar separation of these two isotopes in two algae, *Nitella* and *Valonia* (120); he adduces data tending to support his thesis that this separation is caused by differing partition coefficients of these two isotopes in guiacol-like oil/water systems, but the data for guiacol-water partition are not decisive, the differences being only slightly greater than twice the experimental error. Fenn *et al.* (121) show that among the isotopes of potassium, K^{40} appears in a smaller ratio to K^{39} in human ash than in reagents.

Brooks (122, 123) feels that radioactive ions, here phosphate, do not penetrate isolated cells smoothly, but are taken in and lost repeatedly. The rate of the penetration diminishes with time. The permeability constants (10^6 times *M* per sq. cm. per hr. per gm. *M* per l.) for eggs of *Arbacia punctulata* are 5.3 to 96 in early, and 2.2 to 5.3 in late intake phases. (This omits one divergent result.) Values a little larger for *Asterias forbesi* eggs and for *Fundulus* spp. eggs, for which they are 10^4 times larger, are given. A mathematical formulation for the periodic character of this penetration has been published by Morales (124). Kent (125) demonstrates prompt intake, reversible, of lithium by growing wheat seedlings; from soil containing 18.35 meq. per l. of lithium chloride each plant removes 2.24 to 2.58 μg. per day. Höfler describes changes in the appearance within onion epiderm cells as a result of immersion in calcium chloride (70) and narcosis (shown by stoppages of circulation) by potassium chloride. Although these features form presumptive proof of the penetration of the cations, the proof is not unambiguous. Brooks (126) cites rates of intake of potassium by *Paramecium caudatum* suspended in dilute chloride; they vary fom 0.6 to 2.2 times 10^{-8} *M* per sq. cm. per sec. per gm. per l.

The increased permeability to salts of cells about to divide is correlated with increased permeability to water, and with a lowering of protoplasmic viscosity (68). The toxicity of sodium chloride to the marine amphipod, *Gammarus* sp., is related by Macovski & Macovski (127) to the velocity of the diffusion of the salt. The ab-

sorption of the iron of ferrous ammonium sulfate and of disodium hydrogen arsenate through the honey crop and chitinous cuticulum of bees (128) shows that these toxicants penetrate only through the cuticulum. In the cockroach sodium meta-arsenite seems to be absorbed in the ventriculum (129).

Among the quantitative data are those of Murphy & Shapiro (130) who point out that human erythrocytes undergoing "sickeling" in this type of anemia appear to be about twice as permeable to potassium as normal erythrocytes. Dean (131) uses Rashevsky's equation for permeability (cm. per sec.) or diffusion through an assumed thickness (cm. per sq. cm.). For example, the permeability times 10^{10} to potassium of the erythrocytes of the rabbit is 3.9; man, 4.1; and dog, 11.0; and of dog erythrocytes to sodium, 23.0. The bicarbonate ion either as such or as carbon dioxide has a higher permeability: 2×10^{-5} for ox erythrocytes. A table of comparisons with nonelectrolytes is also given. Figures for the permeability to the radioactive potassium ion (K^{42}) of the erythrocytes of seven vertebrates obtained by Mullins *et al.* (132) gave values after due allowance for the surface area and potassium content as follows: dog, 0.47; man, 2.4; cat and rabbit, 2.6; rat, 4.0; guinea pig, 4.0; and frog, 4.2. This order is different from the crude rate of attainment of complete distribution of potassium, and the authors accept ionic exchange as the mechanism. Davson & Quillian (133) report that when a serum perfusate has excess or deficit of potassium, sodium, or chloride, these ions permeate between the perfusate and the aqueous humor; potassium ions permeate fastest, and sodium ions most slowly with chloride intermediate.

Duryee (134) studied the permeation and effects of salts with various cations and anions on mechanically isolated mature nuclei of amphibia. This study promises well and should merit further attention.

Distribution experiments.—Approximations may be made as to the relative permeabilities of the cells of various tissues by administering a radioactive salt, and observing the time course of the amounts of the labelled ion accumulating. For example, Hevesy & Hahn (135) record that about one-half of the radioactive phosphorus (P^{32}) sodium phosphate, dissolved in plasma and injected intravenously into a rabbit, leaves the blood stream in about one hour, and penetrates fastest into the liver and successively less into the kidney, spleen, heart muscle, small intestine, and brain, and

slowest into skeletal muscles. This refers to concentrations, not to total contents. This order is commonly observed; erythrocytes are generally found to take up ions slowly. But metabolic processes combine this phosphorus in many ways and its later movements have no significance for ion permeability. Tumors are like liver (136, 137). Phosphorus (138 to 142), sodium and phosphate (143), potassium (144, 145, 146), zinc (147, 148, 149), iron (150, 151, 152), iron, cobalt, and manganese (153, 154), iodine (155, 156, 157), arsenic (158, 159), thorium (160), and phospholipid (161) have been studied in this way. Kent & McCance record the rates of absorption and excretion of cobalt, nickel, tin, manganese, silver, gold, lithium, borate, and vanadate (162, 163). The formation of volatile compounds of selenium leads to pulmonary excretion of that element; some details of the distribution of the ion, selenate, in rats are recorded (164).

These distribution studies usually give a measure of permeation through varying epithelia into the blood. The passage of tracer elements into different organs show by their relative rates the relative permeability of the tissues involved; but the varying driving forces and utilization affect the rate of the uptake of one or a closely similar group of elements.

Ion content of the erythrocyte.—Harris (165) treats the maintenance of the ion content of the erythrocyte by its glycolytic metabolism. This obviates the impasse raised by the known permeability of this cell to cations, which seems to invalidate the calculations based on the Gibbs-Donnan equilibrium. However, cations maintained by metabolism can be thought of as among the nonpermeable cations of this theory. Snyder & Katzenellenbogen (166) and Hahn & Hevesy (167) furnish data on the content in the serum and erythrocytes of sodium, potassium, magnesium, calcium, chlorides, and phosphates; the latter discuss the effects of species, temperature, and oxygen use on the phosphate content. Pemphigus tends to increase erythrocyte permeability to sodium (168); the statement is made that "in pemphigus, as in normal subjects, the erythrocyte membrane was found to be impermeable to potassium, and permeable to sodium." This is not generally supported. Smith *et al.* (169) notes that radioactive chloride, bromide, and iodide reach their equilibrium concentrations in less than ten minutes. [See also Dean (131)].

Ion content of muscle.—Manery & Haege (170) compared the

ratios of analytic and tracer chloride of the plasma and organs of the rat and noted the time required for attainment of equality of these ratios. Penetration, within a few minutes, of chloride, was shown for kidney, liver, muscle, cartilage, and tendon. This refers to penetration of chloride into the volume normally occupied by this ion, e.g., in the muscle to the "chloride space." Access to the chloride space of the testis and pyloric mucosa required more than an hour, while the chloride ion entered quickly into the sodium space. For some time it has been apparent that the chloride space of the muscle is not equal to the intercellular space. [Eichelberger *et al.* (171).] Wilde (172) shows that the distribution of chloride fulfills the prediction of the Conway-Boyle membrane equilibrium concept and must penetrate to a definite extent into the muscle fibres. The permeation of potassium is tested by Eichelberger & Roma (173) and by Crismon & Crismon (174) in connection with potassium poisoning of the heart muscle. The amounts of the magnesium ion and calcium in the muscle were determined by Eichelberger *et al.* (171), noting the role of combination. The dependence of the passage of the magnesium ion from the extracellular space into the muscle fibres on the magnesium content of the immersion fluid was studied by Fenn & Haege (175). If this content was less than 1 mM per l., magnesium was lost by the fibres; if more than 4 mM per l., it was taken up; between 1 and 4, no gain or loss was demonstrable. Hevesy & Rebbe (176), noting the distribution of the sodium ion into the sodium space, point out that the phosphate ion was taken up steadily by the frog gastrocnemius muscle, 0.082 mg. per gram of muscle in four days at 22°C., and about one-fifth as much at 0°C. This behavior seems to be due to the transformation of inorganic into organic phosphates, thus maintaining a gradient across the plasma membrane. Dean (177) feels that a "pump" mechanism is necessary to account for the low sodium content of muscle fibres. No details as to the mechanism were offered. The determination of the vascular volume in muscles by the method of Danielli (178) gave the "glucose space" of the frog gastrocnemius a value of 5.2 per cent and of the sartorius 10.5 per cent (179).

Ion content of the cerebrospinal fluid.—Two papers, that of Karlstrom (180) and that of Weir (181), deal with the ratio of the concentrations of chloride and bromide ions of the serum and cerebrospinal fluid. Weir points out that as the bromide content of the

serum varies the ratio also varies. Greenberg *et al.* (182) used radioactive isotopes to measure the rate of passage of these ions from the blood into the cerebrospinal fluid and found this very slow. They feel that secretory activities are involved.

Effects of stimulation, ischemia, and adrenal cortical extracts.—Danielli (183) supposes that the loss of potassium and calcium from the stimulated nerve may be due to a change from relatively wide-spaced to close-packed lipoid molecules of the bimolecular film assumed to be the plasma membrane of the nerve. The closely packed molecules leave open regions where ions may diffuse in or out of the nerve. This picture is correlated with the injury potential difference, initial heat, and accumulation. Cicardo & Torino (184) stimulated curarized dogs and found an increase in blood potassium. Ischemia of muscle masses also increases blood potassium (185), although absence of response in denervated muscle allows a large potassium loss and a little sodium loss (186).

Glandular epithelia, such as that of the submaxillary glands, lose potassium on stimulation (187)—a well established fact. Cicardo (188, 189) and Houssay & Gerschmann (190) show that the gastric and intestinal mucosa lose potassium to the blood on stimulation. The latter authors enrich the intestinal mucosa with potassium by continuous injection of potassium chloride, and also note that ischemia leads to loss of potassium; atropine inhibits loss of potassium and physostigmine prolongs this effect. Epinephrine does not lead to loss of potassium from the intestinal mucosa.

Cicardo (191) adrenalectomized toads (*Bufo arenarium*), so causing loss of 44 per cent of the sodium from the skeletal muscles. Mullins *et al.* (192) found that cortin or desoxycorticosterone reduced the passage of potassium ions into the tissues from the blood, while Darrow (193) found that the latter led to loss of potassium from the heart. Sodium replaced it. Hegnauer (194) reports general loss of potassium as a result of desoxycorticosterone medication, although the erythrocyte or muscle potassium was not decreased by the low blood potassium.

Mutual effects of ions on permeation.—Ions affect each other's penetration in at least two ways: by competition for attraction or adsorption points, and by so affecting the plasma membrane as to restrict or facilitate permeation. The latter may affect molecules as well as ions, and has been discussed above. It is not easy to separate the two effects. Plants commonly display antagonistic phe-

nomena. Gauch & Wadleigh (195) added sodium or calcium chlorides to basic nutrient solutions and found inverse effects of these two cations. Pierre & Bower (196) and Allen (197) record the effects of potassium, calcium, and magnesium on their absorption by crop plants.

The effects of boron on the absorption of major ions have been treated by Briggs (198) and Reeve & Shive (199). That the results are not as clear as one may hope is shown by the findings of Eisenmeyer & Kucinski (200); for example, the addition of calcium salts to a sodium salt medium decreased the sodium content of celery, but increased it in the cabbage.

Bogen (201) reports changes in the permeability of the epidermal cells of *Gentiana cruciata* when they were immersed in various concentrations of several neutral salts. Höfler (70) points out that the addition of small amounts of calcium chloride to isosmotic potassium chloride prevents the appearance of swelling, and decreases in viscosity in epidermis cells of *Allium cepa*, which appear when these cells are put into pure potassium chloride solution. But it is not shown that in this case calcium ions affect permeability to potassium ions. The effects probably result from cytoplasmic reactions. The effects of magnesium and calcium ions in muscle are complicated by the coenzyme action of these ions in the myosin-adenosinetriphosphate reaction (Greville & Lehmann, 202). Danielli (203) attempts to explain completely the antagonistic effects among the physiologically more important ions, notably sodium and calcium. This attempt is based on the quite unwarranted assumption that perfect balance is attained when equal amounts of sodium and calcium ions, for example, are on the surface of the layer of lipoids which is assumed to be the important ingredient of the plasma membrane. For the mechanism of ion binding, invoked by Danielli, see such reviews as that of Greenberg (204).

On the other hand, there are effects not due to the influence of ions on the membrane, but are due to competition for positions, the "adsorption points." Ions are more or less detained at and compete for oppositely charged groups, such as carboxyl, oxygen, hydroxyl, or amines. The clearest presentation is that of Collander (205) who shows the mutual replaceability of potassium, rubidium, and casium, and of calcium and strontium in diverse higher plants. Long (63) notes that sodium chloride decreases the intake of potas-

sium by tomato plants as above. [See also Gauch & Eaton (206)].

The mutual replaceability of cations in animal protoplasm is shown by Steinbach & Spiegelmann (207) who place extruded squid giant nerve axoplasm in Ringer solutions of various potassium contents and note that sodium plus potassium together satisfy a common requirement, and replace each other as their external concentrations vary. Fenn & Haege (175) experimenting on frogs noted competition between the magnesium and potassium ions in penetrating into muscle fibres, ten potassium ions being equivalent to one magnesium ion. Similarly Torda (208) found mutual effects of calcium on the potassium content of striate muscle. Cicardo (191) injected potassium chloride into the toad, and found that the liver lost up to 40 per cent of its sodium content, without change of water content. It will be remembered that this procedure had no effect on the sodium content of the toad muscle. This same principle probably underlies the work of Emmens & Marks (209) in which the toxicity of potassium to mice is shown to be controlled in part by the proportions of sodium and calcium.

Ionic exchange.—A number of workers recognize the general presence of ionic exchange, at least insofar as it involves only inorganic ions. Yeast has long been known as capable of ionic exchange, and recent work shows that *Saccharomyces cereviseae* is permeable to phosphate (210, 211) and potassium (212); all of these workers recognize that these elements are absorbed and released in connection with metabolism. Rothstein & Haege (213) showed that hydrogen ions appeared in the medium while potassium was being absorbed; in the absence of potassium an acid (apparently succinic) appeared slowly in the medium. It is impossible to disprove the thesis that instead of loss of hydrogen ions, a gain of hydroxide ions leads to the observed results. However, the loss of hydrogen seems more probable until the contrary is conclusively shown. Mann (214) observed a metabolism linked with phosphate ion intake in various fungi. Pulver & Verzar (215) and Harris (165) found an analogous relation between the glycolytic metabolism of leucocytes and erythrocytes respectively. The leucocytes took in and metabolized glucose, partly to glycogen, and partly to lower acidic intermediates; human erythrocytes also produce intermediates, perhaps diphosphoglycerates, in connection with the intake of potassium by these cells, or less well of sodium (cf. 84). Similar inorganic ionic exchanges were thought by Brooks

(122, 123) to underlie the intake of alkali metal and phosphate ions. Mullins (216) studied the rate of loss of radioactive sodium and potassium or rubidium ions at various times during their penetration into *Nitella*. When the protoplasm of this alga contains much of one of these ions, it is exchanged slowly and at characteristically different rates when different alkali metal ions were allowed to exchange into the cell for the radioactive ion. When little radioactive ion is present in the cell as a result of loss of this ion, the remainder is lost rapidly, and at a uniform rate. When no salt is provided in the medium, very little of the radioactive ion leaves the cell. These findings are correlated to ionic exchange, the rate of which is dominated by the permeability of the plasma membrane. Many relevant data are included.

Overstreet *et al.* studied cation absorption of excised roots of barley (217) and found that only about 10^{-5} per cent of the ions which have struck the surface of the roots have penetrated into the cells. The authors conclude that the cations must move from adsorption points on soil particles, through the plasma membrane, where similar points must also exist. This is quite consistent with the general concept of ionic exchange, and is further supported by the work of Overstreet *et al.* (218) who studied the absorption of bicarbonate ions, containing radioactive carbon, and potassium, much less of the former being taken in by barley roots.

The work of Fenn's laboratory is based on this concept, and is especially well shown by work on the erythrocytes (132). Furchgott & Shorr (142) show that radioactive phosphate enters without organic reaction into dog heart muscle cells, its entrance curve being exponential. Barker, Furchgott & Shorr (219) point out that this entrance involves equal and opposite movement of inactive phosphate.

Accumulation and secretion.—These processes are similar in that material is being moved against its activity gradient by utilization of energy derived from metabolism. The way in which this energy is utilized is not well established in any case, and exceptions to this definition may well be quoted. It has been suggested by Brooks (126) that accumulation of cations may involve ionic exchange for the ammonium ion, the dynamic size and properties of which resemble those of potassium. In plant nutrition it is not clear as to whether this ion or ammonia can be converted to nitrate in the medium; this oxidation is requisite for continued accumulation.

Brooks points out that for *Paramecium*, the amount of potassium taken in was between 2.2 and 5.5 per cent of the ammonium and ammonia liberated, a figure consistent with the probable amount of the ammonium ion in the ciliate. The utility of thus eliminating a substance so toxic to animal cells and to plants (220), its presence within living cells (221, 222), and the tendency of higher plants to absorb it in smaller amounts than those of nitrate are well established (223), and favor such a formulation. It is well known that something else besides hydrogen ions is requisite in crop plant ion accumulation, but it has been seen above (165, 213, 214, 215) that hydrogen ions can play the same role as other counter ions for potassium, etc. [See also the work of various authors (224, 225, 226).] It may be possible for living cells to acquire their quota of inorganic ions by ionic exchange for ammonium, hydrogen, or similar counter ions ("primary accumulation"), and independent of loss of mineral ions ("induced accumulation"). If ionic exchange is vital for accumulation, the paper by Viets (227) is understandable. He found that addition of calcium sulfate to a potassium bromide solution caused barley roots to accumulate more of the latter. Potassium bromide is known to increase permeability greatly (e.g., Osterhout's work), and calcium to restrain this increase, and hence promote accumulation by favoring ionic exchange.

Collander (228) feels that ordinary diffusion processes are inadequate to explain accumulation of ions in plants, and that "adenoid activity" offers the probable explanation. However, this depends upon the interpretation put on these terms, and need not conflict with the above. The occurrence of accumulation of ions by the alga, *Chlorella pyrenoidosa*, was noted by Scott (229). Steward *et al.* (230) localizes this process in the terminal centimeter of barley roots, its activity diminishing strongly in successive regions. Gauch & Eaton note relations between sugar content of barley roots and ion intake (206).

The most provocative concept in this field is that of Lundegårdh (231) that two types of respiration can be found in plant roots, one the "anion respiration" and a "fundamental respiration" not directly involved in ion respiration. He measures potential differences of about fifty or sixty millivolts between plant roots and the medium, and attributes the potential difference to organic phosphates to which cations are passively attracted. The anion

respiration, in contrast to this fundamental respiration, is aerobic, and results in anion intake, leading to further passive attraction of cations. The nature of sugars provided in the medium leads to variable depression of the observed potential differences (232), and anions also affect it (233, 234). These concepts have led to a spirited controversy, for example, with Steward & Berry (235). Robertson (236) adopts this idea of "extra respiration" in his work on the carrot root, but suggests that ions enter the protoplasm only passively, the energy being used in transferring them to the vacuoles.

Hoagland & Broyer (237) show that the metabolic processes needed for ion accumulation are aerobic. Steward *et al.* (222, 238 to 241) made painstaking studies of the details of metabolism of potato slices during ion accumulation, and find that primary accumulation is most closely correlated with protein synthesis and aerobic carbon dioxide production. Protein synthesis is linked with oxidative deamination, which produces ammonia and acids. Effects of ions, of temperature, etc., were closely studied. Wood (242) adopts a modern viewpoint in his studies of plant metabolism.

Considering the problem of secretion in animals, we find that Schmidt-Nielsen (243) follows Lundegårdh in discriminating between distinct respiration for intake of cations and anions by the basal part of the gills of marine crustaceans. These epithelia can discriminate between sodium and potassium cations, but not perceptibly between chloride, bromide, and sulfocyanide anions.

The review of Gray (244) of the secretion of gastric juice approaches a solution of this mechanism. There is more doubt as to this mechanism for the secretion of saliva (245, 246, 247), the formation of the cerebrospinal fluid, for which Greenberg *et al.* favors the participation of secretion (182), and the migration of sodium in cat erythrocytes, attributed by Davson (248) to an enzyme. [See Höber (101) and Visscher (102).]

Electrical properties.—Osterhout (249) sought the basis for variations of potential differences induced in the algae *Nitella* and *Valonia* by changes from media containing the sodium ion to media containing potassium ion—the "potassium effect." He attributes this to changes in permeability of the plasma and vacuolar membranes, staggered in part due to the delay in penetration of the new ions to the vacuolar membrane. Similar reasoning is used in

his studies of action potential curves in the related alga, *Chara* (250) and *Nitella* (251). Abolition of this effect by guaiacol, hexylresorcinol, benzene, and nitrobenzene was examined (252, 253, 254), and also the capacity of ammonia to reduce the potential effect produced by aniline in *Valonia* (255). From this point of view substances, whose removal by leaching out of *Nitella* abolishes the potassium effect, are replaced by guanidine hydrochloride (256).

Much study has been devoted to the impedance of living tissues to alternating current as a measure of ionic permeability. The effects of salts on impedance of tissues have been reported (257, 258). See also the review by Gerard (259).

Gerstner (32) made a significant study of the parallel ionic permeability and impedance of symmetrical halves of frog abdominal skins. He finds good correlation for frequencies of about one to four hundred cycles per second, using series capacitance. The correlation at two hundred cycles between sulfocyanide penetration through the skin and the conductance was 0.93. Poznanskaya (260) did experiments of this type. This finding validates Osterhout's earlier studies of conductance as a measure of permeability of *Laminaria* (a marine alga); they were based on sixty cycle current measurements.

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THE PHYSICAL PROPERTIES OF PROTOPLASM

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Introduction.—A review of theoretical research in a field of science, the immediate practical application of which is slight, offers little encouragement to the reviewer in times of war. Yet the situation is not quite as bad as it might seem, for there has been one very fertile field of publication during the past few years which offers ample material for a reviewer. Numerous textbooks, monographs, symposia, and handbooks in biology and medicine have appeared. To be sure, these are in themselves reviews, but they include much new and original work, especially in the realm of interpretation. Among them are the excellent collection of papers edited by Hoerr (1) and published in honor of Professor Bensley; the symposium on *The Cell and Protoplasm* held at Stanford University, and edited by Taylor (2); the stupendous work, entitled *Medical Physics*, edited by Glasser (3); the text by Pfeiffer (4) on experimental cytology; Guilliermond's (5) *Cytoplasm of the Plant Cell;* and the symposium on *The Structure of Protoplasm*, edited by Seifriz (6). Among these, I should like to single out for the moment the large volume on *Medical Physics* edited by Glasser (3). This book is certain to be of great interest and help to all workers in physiology, medicine, and biology. With the exception of one or two weak chapters the contributions of the two hundred and fifty-five authors are well done. The subjects treated are mostly medical or with medical application, and a number of chapters are of strictly biological import, such as those on bioelectricity, electrical physiology, electrophoresis, mitogenetic radiation, osmosis, and protoplasm.

Viscosity.—Viscosity, that classical property of protoplasm which started several protoplasmologists on their life work, has been sorely neglected in recent years, but this, in the reviewer's opinion, is a fortunate circumstance, for viscosity, like surface tension, permeability, Donnan equilibrium, and antagonism of the past twenty-five years, has been greatly overemphasized as a cause of cellular processes. Changes in viscosity, surface tension, permeability, etc. are significant properties of living matter and come

into play in many vital processes, but they are more often the result of or incidental to the phenomenon of which they are said to be the cause. To cite but one example, when protoplasmic flow is diminished or stopped by an experimental condition, the assumption is frequently made that an increase in viscosity has occurred and that this increase is responsible for the decreased flow. The rate of protoplasmic movement depends upon two major factors, viscosity and motivé force. One or the other or both may be responsible for a change in rate of streaming. The situation may be compared to water flowing through a pipe-line under pressure exerted by a pump. If the pump breaks down and flow stops, the viscosity of the water has not therefore increased. Kamiya (7) has found it possible to stop protoplasmic streaming by mechanical pressure without any change in viscosity occurring.

Some work on protoplasmic consistency has been reported; thus, Angerer & Wilbur (8) studied the effects of electrical fields on the relative viscosity of the plasma gel of the amoeba. Northen (9) has continued his studies on the structural viscosity of protoplasm.

A significant feature of protoplasmic consistency which the biologist should always bear in mind is the anomalous flow of organic liquids. Experimental proof of the non-Newtonian character of protoplasm is very meager though it has been reported by Pfeiffer (10); he has shown that flowing protoplasm when viewed between crossed nicols is seen to be anisotropic, that its flow within a capillary is anomalous and therefore not obedient to the laws of Newton, Poiseuille, and Stokes, and that the structural features responsible for the refractive behavior of protoplasm are also responsible for its non-Newtonian behavior. That protoplasm belongs to the large group of organic substances which are non-Newtonian in behavior has been repeatedly emphasized by Seifriz (11).

Many of the physical properties of protoplasm are so closely correlated, so intimately interdependent that to mention one is to imply the others. This is true of the non-Newtonian behavior of protoplasm in its relation to double refraction, elasticity, and protoplasmic structure. The first of these is frequently denied because it is not readily demonstrated, but Schmidt (12) has done so indubitably.

The significance of flow-birefringence in experimental morphol-

ogy and cytology is thoroughly discussed by Needham and co-authors and will be presented here under the section on structure.

Elasticity.—The importance of elasticity in protoplasmic studies has long been emphasized by Scarth (13) and Seifriz (14). In Scarth's words, "elasticity is the chief quality of protoplasm on which a conjecture of the ultramicroscopic structure of living matter can be based."

Norris (15) has reviewed work on the physical properties of living matter. From his studies (16) on the elasticity of the nucleated erythrocyte of the newt he demonstrates the presence of a membrane which he regards as the shape-supporting structure of the cell as a whole. His demonstration of the presence of an erythrocyte membrane is in support of similar work by others (17).

In continuing his studies on protoplasmic elasticity Norris (18) made a determination of Young's modulus for a strand of *Myxomycete plasmodium*. The amount of bending of a calibrated needle with which the protoplasm is being stretched is a measure of the force exerted. He found the modulus of elasticity for strands of *Physarum* to be 9.0×10^4 dynes per sq. cm. at room temperature for increases in length up to 40 per cent. When the temperature was lowered to 10°C., there was an increase in the average value of Young's modulus to over twice that found at room temperature; the strands no longer followed Hooke's law. With increases in temperature the value of Young's modulus was lowered.

A very important observation by Pease (19), one answering a long controversy, was that bearing on the place where the material responsible for the elasticity of protoplasm is situated; it is not concentrated at the surface, as shown by tests with saponin. Pease noted also that chloretone anesthesia has no effect on the elasticity of *Physarum* strands, although streaming is reversibly stopped. One looks forward with anticipation to more work of this quality by Norris and Pease.

Sinoto & Sato (20) studied changes in cytoplasmic elasticity in *Spirogyra*.

Contractility.—Contractility is a protoplasmic property closely related to elasticity. Seifriz (21) attaches much importance to it, particularly to rhythmic contractility (22) which he regards as a potential property of all protoplasm manifesting itself only in tissue where it is needed, as in heart muscle, intestines, and the diaphragm; it is further to be seen in many forms of cellular activity,

in the migration of fibroblasts, in protozoan flagellae, and in myxomycetes (23).

Spirality.—The spiral characteristics of living matter have been but little studied, yet some observations and general conclusions have been made (24).

Castle (25), by automatic photographic recording, studied the elongational and rotational, that is to say, spiral, components of growth of the sporangiophore of *Phycomyces.*

That protoplasm should exhibit spiral tendencies is obvious from the asymmetry of both organisms and crystalline matter. To what extent spiral movement as in protozoa, spiral growth as in horns, tusks, and trees, and spiral shapes as in chromosomes can be attributed to the asymmetry of crystals, or to the asymmetry of the carbon atom, or the helical organic molecules is a matter of conjecture, but spirality in living matter is there nevertheless, and in many forms.

Torsion.—That a state of torsion may exist in protoplasm has recently been demonstrated in the reviewer's laboratory; its correlation to protoplasmic streaming has also been demonstrated. The work is not complete but promises some interesting discoveries.

That protoplasm should exist in a state of torsion is an obvious deduction on purely theoretical grounds; if there is a twist in protoplasm, i.e. spirality or asymmetry, then any movement, such as protoplasmic streaming, should set up a state of torsion, and this is what takes place.

Structure.—All problems having to do with the physical properties of protoplasm ultimately lead to structure. This is inevitable, for structure determines these properties. There are certain physiological functions such as respiration and photosynthesis which may be elucidated to a fair degree without reference to structure, but in the last analysis these, too, are problems in structure.

Protoplasmic structure is of four categories, gross structure or cellular organization, microscopic and therefore visible structure, ultramicroscopic or colloidal structure, and molecular structure.

Scarth (26) has handled the coarser structure of protoplasm, or cell organization, unusually well, and clarified the confusion which has arisen in the application of term after term to the surface layer of protoplasm. Scarth distinguishes five layers or oriented substances, which, though they apply to the plant cell, may fit the animal cell as well, with the exception of the outermost wall of

cellulose in plants. Within the cellulose wall there are, in order, the protoplasmic membrane or ectoplast, the plasma gel or cortical endoplasm, the plasmasol or liquid endoplasm, and the inner tonoplast or vacuolar membrane surrounding the vacuolar fluid; through which kinoplasmic strands thread their way, joining the outer membrane with the tonoplast.

The presence of and need for cellular organization has been appreciated by many workers. Cohn (27) discusses the arrangement of the component parts of cells into patterns. Nonpolarized organisms have no fixed axis of development. Polarization may be induced in initially unpolarized forms, e.g., *Myxomycetes* and *Aerasieae*, by an asymmetric environment.

Parvulescu (28) discusses the organization of living matter, and Gause (29) considers the possible application of some organization concepts of topology to the asymmetric organization of protoplasm.

Skotnicky (30) states that the conducting layer of nerves is a property of the functional organization of protoplasm.

The microscopically visible structure of protoplasm has been treated so many times that the theories are now classical. Little new has been added, chiefly because it is now generally recognized that the visible structure of protoplasm has nothing to do with the basic structure. For many years the reviewer (11) has emphasized that, although the visible emulsion in protoplasm is of importance from the point of view of nutrition, it is in no way responsible for such properties of protoplasm as permeability, imbibition, elasticity, or electric conduction, nor can it in any way represent that structure of living matter which distinguishes it from the nonliving. The visible structure is not, as has in the past been said, a coarser manifestation of the finer structure which lies hidden from view. This denial does not imply that the visible structure should be ignored for it plays a significant role in the metabolism of life, just as does the still coarser organization of the cell as a whole.

Beyond the limit of microscopic visibility, and to some extent still within it, lies the colloidal structure of protoplasm. This is, in part, a fine emulsion which, in its purest form, consists of minute hyaline globules dispersed in a translucent optically empty matrix. The contents of the minute globules was termed "phaneroplasm" by the reviewer, and the matrix was named "cryptoplasm," which is probably synonymous with the substance Scarth calls kino-

plasm. The optically empty matrix, the cryptoplasm or kinoplasm, represents protoplasm in its purest, simplest form. It is its structure which concerns us now. No structure is visible in the hyaline matrix of protoplasm. The structure must, therefore, be interpreted, and in terms of molecules.

The molecular structure of protoplasm has been given much serious thought by a number of biologists with the collaboration of able physical chemists among whom are Fruendlich (31), Astbury (32, Meyer (33), Mark (34), Pauling (35, 36), and Banga & Szent-Györgyi (37).

Biologists in their interpretation of protoplasmic structure have done no more than apply to living matter accepted theories of the structure of organic matter, of proteins, cellulose, rubber, and wool. To such a correlation there is some strong antagonism which apparently involves opposition to any interpretation of the invisible structure of living matter. Investigations and hypotheses on protoplasmic structure are termed futile, just as were the experiments of Pasteur and Roentgen, and much other pioneer work in science. The opinion that studies on and interpretations of the molecular structure of protoplasm are futile is held by some chemists who are having difficulty with the structure of proteins, enzymes, and pigments. It is their belief that any attempt to interpret protoplasmic structure must wait until work on nonliving systems is completed. To this advice there are three replies: their work will never be done and protoplasmologists are not willing to wait that long; no branch of science has ever waited for another to advance; it is often the less well grounded sciences which show the more exact sciences the road to follow, proof of which lies in the history of osmosis, ionization, the solution laws, pH, hormones,vitamins, and viruses. In each of these subjects the biologist set the problem and went quite a way with it, and at that point the chemist took it up. In the same way, the biologist will continue his studies on the molecular structure of protoplasm grateful for the help of many able physicists and chemists and not much minding the destructive comments of a few.

Among the pioneer workers on protoplasmic structure is Bensley (38) whose work bears primarily on the chemical constitution of protoplasm. His procedure was an ingenious one. He sought to obtain from the cell what others had avoided because of the difficulties of solubility. Using frozen dried material Bensley

& Hoerr (39) were able to introduce solvent solutions into a chemically unaltered cell. In such preparations of the liver of the guinea pig sodium chloride quickly dissolved the mobile protein of the cell but left behind a morphologically complete cell. Treatment with ammonia solution removed the mitochondria and nuclear chromatin but left the cell membrane, cytoplasmic substrate, nuclear membrane, and linin threads. The cytoplasmic residue was termed structural protein. On repeated solution and precipitation with strong alkali a material named ellipsin was obtained. Later Bensley (40) reported the discovery of a sodium chloride soluble component of ellipsin, a highly viscous substance with pronounced elastic properties containing discrete fibers of great length. This he called plasmosin, regarding it as the structural foundation of tissue very much as is myosin in muscle.

Banga & Szent-Györgyi (37) obtained a similar viscous extract from kidney which precipitated in fibrous form and gave an x-ray diagram like that of myosin-B.

Purification of plasmosin by Lazarow (41) led to the discovery that plasmosin is a nucleoprotein, a fact which would suggest its origin from the nucleus. The idea that nucleoproteins are confined to the nucleus has, however, been breaking down owing to the discovery that many active components of cells have a nucleotide structure and the discovery of Claude (42) that the particulates contain nucleoprotein. Without rejecting the idea that the nuclei contain plasmosin, Bensley (40) believes that it is in large measure a constituent of cytoplasm. Whether it originates there or is produced in the nucleus is, of course, a topic for speculation and research.

In contradiction to the foregoing conclusion as to the seat of origin of plasmosin Mirsky & Pollister (43) insist that the preponderance of the evidence indicates that the great bulk of fibrous nucleoprotein comes from the nucleus, and that the cytoplasm can at most contain only traces of it. Furthermore, it is also maintained that this fibrous precipitate extracted by Bensley from cells only superficially resembles the well known fibrous cytoplasmic protein myosin, but conforms very closely to substances known to come from cell nuclei.

The work of Bensley and his collaborators leads to the concept of a fibrous structure of the basic constituents of protoplasm. This is the point of view now generally held by the majority of workers.

Such a view may in time lead to the discarding of that *bête noir* of colloidal and biological structural chemistry, the word "emulsoid" (44). Strange to say, it is being retained by a small group of chemists probably as a habit in spite of its misleading implications. Well informed chemists have rejected the word with all its erroneous connotations. Both the living and all nonliving jellies are not "like emulsions." They are built of fibrous units such as the molecular chain of cellulose and the polypeptide chain of proteins.

Though the protein chain has long been known, it was the cellulose fiber which first made biologists, and certain chemists, fully conscious of the fibrous structure of protoplasm. The outstanding workers in this field were Sponsler (45), Meyer (46), and Mark (47). That the coarser structure of natural cellulose is fibrous, the component parts being long and tenuous threads just as are the molecules of which they are made, is nicely shown by dissection work of the cell wall by Hock (48). Soon, however, work on proteins replaced that on cellulose in its bearing on the problem of protoplasmic structure. Roentgenographic work on nerve, muscle, sinew, hair, chitin, and wool has taken the center of the stage in its biological implications. Earlier studies on the structural basis of elastic qualities in proteins had indicated that helical molecules were responsible. This and other hypotheses, notably in connection with rubber, as possible interpretations of the contractility of tissue have not been wholly discarded, but it is rather the folded protein chain so well pictured by Astbury (49) which is now generally accepted as the structural molecular basis of elastic and contractile properties in protoplasm and nonliving organic matter.

Into this rather well substantiated view of protoplasmic structure, there have crept some novel features, certain ones of which are enlightening, others disturbing though not seriously so. Among the latter is the concept of the spherical molecule so ardently supported by Wrinch (50) To build a structure possessing elastic and related qualities out of spherical units is impossible. Comparison may be made to a sand pile, on the one hand, and to a brush heap on the other hand; the latter not the former, is elastic. Meyer (51) has shown that certain protein molecules for which a spherical form has been claimed cannot be so. Lecomte du Noüy (52) likewise believes that the existence of oriented albumin which has been demonstrated by him, Devaux, and Langmuir, contradicts the spherical shape. Lecomte du Noüy regards the albumin molecule as short

but prismatic in shape. Banga & Szent-Györgyi (37) tentatively settled the controversy by assuming that,

> whenever nature needs a mobile protein (serum albumin and globulin, secretions like milk-proteins, hormones like insulin, different enzymes, etc.) it applies the globular shape, and whenever it wants to build a solid structure it applies the rod shape. Proteins have been found to be mostly globular because unconsciously the mobile and more easily accessible proteins have been selected for study.

The whole subject of protoplasmic structure, both the historical view and the modern interpretations based on x-ray studies, has been reviewed a number of times by Seifriz (11, 14).

In all branches of science there are investigators who are in one field very able men but in another overenthusiastic, or the field is too foreign to that in which they have built a real and substantial reputation. In this category belongs Sleggs (53) from whom have come, by the very last post, self-published accounts of his work which can only be characterized as overenthusiastic advertisements of his moiré theory of protoplasmic structure. Ordinarily one would disregard such publications, but as there is a strong element of truth in them one cannot let the Irish humor they contain obscure the truth. Though Astbury may cringe at the comparison, Sleggs' crossed grids are not unlike Astbury's (54) parallel alignment of grids resulting in a three-dimensional lattice. Perhaps Astbury's work is the source of Sleggs' conceptions, as is the work of numerous stereochemists and biologists.

The phenomenon of thixotrophy has been applied to interpretations of biological processes rather frequently (23). Copley (55) does so in discussing hemophilic and heparinized blood.

The most significant fact to be noted in regard to protoplasmic structure is its continuity (14), and as corollaries to this are the linear unit and the lateral bond. Much has been said on the first two of these problems, but the third, though by no means neglected in the past, is receiving special attention at present. Seifriz (56) emphasizes the importance of the lateral bond to biology, especially its varying degree of firmness, and Pauling (35) as chemist, selects one of the most significant of lateral ties, the hydrogen bond, which he regards as of greater significance to physiology than any other single structural feature.

One basic problem in structural chemistry which is of fundamental importance to biology and involves lateral bonds is the maintenance in protein dispersions and in protoplasm of two ap-

parently incompatible properties, the capacity to flow and the possession of structural qualities necessary to satisfy elasticity and tensile strength. Loosely attached cross-linkages, such as those established by the hydrogen bond, satisfy this requirement.

Certain other not necessarily divergent views of protoplasmic structure have been presented. Notable among these is that based on coacervates, a concept and term coined by Bungenberg de Jong (57, 58). In a coacervate, according to Bungenberg de Jong, the colloidal units are attracted by electrostatic forces but kept apart by solvation. Thus, the aggregate, although coherent, may be quite fluid. Dufrenov (59) describes the formation of coacervates in the vacuoles of hypoplastic cells as due to a change in the equilibrium between the diffused colloidal material and the surrounding liquid.

Scarth (26) perhaps more than any other scientist, has emphasized the significance of the coacervate concept for biology. Without directly quoting him, the reviewer will nevertheless express what he believes to be Scarth's views on the reasons and needs of the coacervate point of view in chemistry and biology. According to Scarth, a coacervate is a liquid aggregate of lyophilic colloidal matter which is liquid by virtue of solvation and not because the nonsolvated substance is liquid. Although the phenomenon of droplet precipitates and the like has long been known, the coacervate concept is new in that it identifies by name and interpretation a state of matter which lies between sol and gel. As the coacervate concept is new and suggestive, we may, with Scarth, elaborate a little further. The three degrees of freedom of movement possessed by molecules in gases, liquids, and solids respectively, are possessed by colloidal units in sols, coacervates, and gels respectively. In a sol there is complete freedom of the colloidal particles, in a gel there is no freedom, and in a coacervate there is freedom to move around but not away from the surrounding particles. It is a simplification to reduce the colloidal states of matter to three, namely, sol, coacervate, and gel, but this is true of the three physical states, gas, liquid, and solid; in both cases the simplification is theoretically fundamental. The three colloidal states may be restated as dispersed state, liquid aggregate, and solid aggregate.

There can be no question as to the reality of the problem which the coacervate concept attempts, with fair success, to solve, but to the reviewer it is merely another view of a problem long expressed

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and solved with perhaps more success by the concept of shifting lateral bonds. In his book on protoplasm, Seifriz (6) states that if protein molecules are long chains with lateral bonds of unsatisfied valences or ionized radicals, then the necessary requirements of an elastic brush heap held together by weak shifting ties is met. One may then view the whole as possessing no individual molecules, or it is itself one colossal molecule. Such a brush heap of molecular fibers tied by loose shifting bonds satisfies the structural requirements of an elastic semirigid liquid. It meets also the requirements of a thixotropic gel of high water content such as is protoplasm.

The foregoing was written in 1932 and the ideas on which it is based were then a decade old. It represented the point of view of Freundlich and others abroad, and of J. A. Wilson and others in America. Reviewing this problem again today, the same general viewpoint still prevails, with one helpful additional concept, that of the hydrogen bond. The coacervate hypothesis is another answer to the same general problem.

The student of protoplasmic structure should not restrict his reading to biological journals, for much of the research which is helpful to him, indeed which is the basis of his interpretations, is in chemical and physical papers. Such are the articles on the viscosity, structure, molecular weight, and polymerization of cellulose (60), and especially the articles on fibrous and corpuscular proteins (61). Certain others are in biological journals but strictly chemical in presentation. The whole concept of protoplasmic structure must start with relatively simple organic components such as starch (62) and proceed through cellulose, proteins, chitin, wool, sinew, to muscle and nerve which are protoplasm.

Lawrence, Needham, and collaborators (63, 64, 65) have published a series of papers on anomalous viscosity flow-birefringence, and protoplasmic structure wherein they emphasize the interrelationship of these properties in living matter. They state that their work is based on the belief that the shapes of molecules, especially proteins, may throw light upon the nature of morphological and histological shapes, and the changes which they undergo. Their first paper (63) presents a description of apparatus whereby the flow-birefringence and the relative viscosity of a protein solution may be measured and its anomalous viscosity assessed, careful distinction being made between effects due to the bulk phase and those due to the surface film at the air-water interface. In their

second paper (64) the authors discuss their experimental results and come to these conclusions: that the proteins studied may be divided into three major groups: Group 1 consists of those proteins which show flow-anomaly both in the bulk phase and in the surface film. These also show flow-birefringence in the bulk phase. Examples are tobacco mosaic, disease virus nucleoprotein, and myosin. Though corpuscular proteins, they have elongated particles before denaturation. Group 2 consists of those proteins which show flow-anomaly only in the surface film, and no flow-birefringence in the bulk phase. They are probably close to spherical in shape in solution but form elongated particles as they denature in the surface film. After this process has been completed, they may show flow-anomaly also in the bulk phase. An example is serum euglobulin. Group 3 consists of those proteins which show flow-anomaly neither in the bulk phase nor in the surface film. They are probably close to spherical in shape. Examples are insulin, and methemoglobin, amphibian embryo euglobulin-c, and mucoproteins. In their third paper (65) the authors reemphasize the theoretical significance of protein fiber molecules in relation to experimental morphology and cytology. The paper deals with results of an intensive study of the particle shape of myosin, the globulin of muscle, by the methods of anomalous viscosity and flow-birefringence.

Colloidial phenomena.—Many of the activities which take place in protoplasm can be characterized as colloidal. Coagulation is the most common of these, but the coagulum is not always the same; it may be fine, coarse, granular, fibrous, or of other configuration. One of the more unusual forms of protoplasmic coagulation which may occur at death is that resulting in the precipitation of Liesegang rings. This has been reported as occurring in slime molds by Uraguchi (66). The rings are produced by the salts of heavy metals. Küster (67) likewise reports rhythmic banding produced by dyes in the cell wall of plants.

That protoplasm is sometimes fluid and sometimes firm is a truism. The change from one to the other state is known as sol-gel reversibility. This phenomenon, so common in colloidal matter, served Mast (68) as the basis of his now quite famous sol-gel theory of ameboid movement. The theory was advanced nearly twenty years ago and gains support through application in recent

studies by Marsland (69) on the effects of hydrostatic pressure on protoplasmic streaming and sol-gel equilibria, and by Lewis (70) on the ameboid motion of fibroblasts.

Among colloidal phenomena are electrokinetic ones, in particular the migration of cells in an electric field. Much can be learned of the nature of the surface layer of cells by this method. Moyer's (71) brilliant work on species relationship in *Euphoribias* is an example. Most of this type of research has been recently assembled by Abramson, Moyer & Gorin (72).

Permeability.—The selective permeability of cells is handled in this volume as a separate subject, but it is as much a problem in protoplasmic structure as it is in permeability. Mechanisms which explain cellular permeability are among the physical properties of protoplasm. Thus, a sieve is a purely mechanical means of accomplishing selective permeability. The making of models which emulate the behavior of the cell membrane is a problem in the physical nature of protoplasm. Here it may be emphasized that the cell membrane is protoplasm, a fact often overlooked. Sollner & Carr (73) have published a series of articles on the structure and electrical behavior of collodium membranes which bear on protoplasmic permeability.

The only recent work on permeability to which the reviewer would like to devote a little space is that of Lundegardh (74). He denies the speculation that materials enter cells only as molecules. The reviewer has long felt that in the face of the modern concept of the complete ionization of salts, even at high concentrations which are never reached in the soil, it is impossible that elements should enter cells as molecules for there are not any molecules present. To call attention to the fact that carbon dioxide is a weak electrolyte and therefore but partially dissociated is of no avail, for carbon dioxide is but one of many substances which enter cells. Lundegardh says, "If the cell or organ is placed in contact with a solution of a single salt, full equivalency in the absorption of cations and anions is an exception. . . . These experiments show that the salt is not taken up as molecules. . . ."

Mechanical forces.—Biological research usually takes the form of a study of the effects on living matter of applied chemicals and other extraneous influences such as pressure, heat, and light. Among these are various mechanical forces among which are

gravity, centrifugal force, and pressure, both mechanical and hydrostatic. These may be continuously or intermittently, gradually or suddenly applied.

That living matter responds to gravity is evident from such common vital phenomena as geotropism in plants. The extent to which protoplasm as such responds to gravitational force is a moot question to which the usual answer is negative; thus Luyet & Gehenio (75) state that the orientation of the branches developing from transplants of the myxomycete *Physarum* when placed on vertical agar plates is random.

The influence of centrifugal force on protoplasm is likewise a disputed question and a far more controversial one. There are the contradictory experiments of Svedberg and of Nêmec, though the difference in kind of material may be responsible for the divergent results. Svedberg centrifuged protozoa at very high speeds and no damage resulted. Nêmec found dividing cells very sensitive to centrifugal force.

In contradiction to the long held assumption of Heilbrunn (76), Weber (77), and others, Küster (78) found a decrease in the viscosity of *Cladophora* protoplasm due to centrifugal force. He suggests that it is not higher speeds which produce abnormal changes but fractional centrifugation.

Kamiya (79) noted distortion in the position of the lateral walls of *Spirogyra* when centrifuged, and complete interruption of the formation of the walls. Shimamura (80) reports that centrifugal force does not suspend nuclear division but merely distorts the figure. His work gives substantial evidence of the presence of spindle fibers in living material, a fact occasionally denied by some modern workers.

Mechanical and hydrostatic pressures when applied suddenly, producing shock, have quite other effects than when slowly and continuously applied. Thus, easing protoplasm into water has no effect, but plunging it in has the effect of shock and will stop the streaming of protoplasm.

Pease (81) subjected portions of the plasmodium of slime molds to hydrostatic pressures of 1000 to 3000 pounds per square inch, and observed a great acceleration in rate of protoplasmic flow. An increase in rate of streaming over the normal maximum is very rare in myxomycetes. Pease also noted violent contortions of the protoplasm with each pressure change. A hydrostatic pressure of

4000 pounds is critical, flow is greatly retarded, and disorganization is general. Pease believes that his observations support the theory that protoplasmic streaming results from local rhythmical contractions of the plasmogel.

Harvey (82) has made similar studies of the effect of pressure on *Nitella*. Johnson, Brown & Marsland (83) have correlated the biological effects of temperature, pressure, and narcotics on bacterial luminescence.

Salts.—The naturally occurring and artificially applied environmental factors which have been studied in regard to their effects on protoplasm are so numerous that each would require individual chapters. Of these substances, brief reference may be made to salts. The emphasis placed by Heilbrunn (76) on the role of calcium would make this element the outstanding one in animal life, to which Chambers (84) adds some support. In contrast is the emphasis Barnes (85) lays on sodium as a vital element. Many years ago Ringer found sodium to be an essential element in maintaining the pulsation of an extirpated heart, and if calcium is added the artificial beat is prolonged. Both elements are necessary to life.

Temperature.—The effects of temperature on protoplasm deserve more attention than has been given them. Some thorough work has been done but there is little interpretation. Lack of interpretation is particularly evident in the many, many determinations of temperature coefficients which have been made with little knowledge of what they signify. Some few such measurements are desirable so that they may be correlated with similar ones of chemical reactions in nonliving material, but to add determination after determination of temperature coefficients is an endless and useless task. Pure quantitative data presented without interpretation contribute far less to the advancement of science than do qualitative observations which have at least the virtue of some thought if not of many numbers.

Luyet (75) has done thorough work on the effects of cold on protoplasm. He finds an average of $-0.17°$C. to be the freezing point of the living plasmodium of slime molds. When slime mold protoplasm is exposed to cold, movement ceases at 5°, hyaline vesicles are formed at 3°, disorganization takes place at 0°. If the freezing point is quickly reached, the ice crystals formed are small and the protoplast will recover. If the freezing point is slowly reached, the crystals formed are large and the protoplast is killed.

Gehenio (86) reports that dead tissue usually has a higher freezing point than living tissue, but the protoplasm of the slime mold *Physarum* consistently showed a lower freezing point after death. The freezing point value for dead protoplasm is −0.37°C., and for living, −0.25°C.

A particularly interesting application of heat and cold to protoplasm is that of anesthesia. Work in the reviewer's laboratory indicates that between 2° and 0°C. a state of anesthesia sets in and is maintained until warmth is restored. The organism used was the slime mold *Physarum* and the indication of anesthesia was a cessation of protoplasmic flow. Heat, likewise, will bring on a state of suspended animation at 43°C.; recovery follows if the heat has been cautiously applied. As an anesthetic agent heat is much less successful than cold.

Electrical forces.—Again we treat of a subject that has surged ahead of late at so rapid and dramatic a rate that it can be touched upon but lightly in the space at our disposal. When one recalls the rather modest claims made by Crile ten years ago and how thoroughly he was condemned for them, one cannot help but marvel at man's unwillingness to accept, yes, to listen to a speculation which a decade later is not only accepted but already outmoded. The basic claim of Crile was simply that the organism is a physical-chemical entity; it obeys the principles of cause and effect; its activity stems from the release of energy in oxidation; this energy may take the form of electrical energy; vital processes may, therefore, be explained in terms of electrical potentials; the organism is a bipolar mechanism; electrical potential differences within and between systems produce all physical and mental activities; measurements of such potentials yield clues as to the state of the mechanism as a whole. These are prophetic assertions and modest ones when compared with the almost sensational measurements of brain potentials by Burr & Northrup (87), Burr (88), Harvey (89), and others (90, 91) now generally accepted as commonplace research in physiology. Particularly impressive are the correlations between the brain potentials and the patient's physiological and psychological state.

Whatever one's opinion may be on specific experimental work, the undeniable fact remains that any system containing selectively permeable membranes bathed in electrolytes is certain to have

potential differences due to an unequal distribution of ions. Such potentials must exist within living cells and between one cell and another. The further fact that different regions in a cell are more or less independently engaged in different physiological activities suggests that their ionic activities differ, which is but to say that their electrical activities differ and that there are therefore potential differences between them.

One interesting form of application of electrical forces to protoplasm is that of electrical shock, particularly its effect on such properties as cyclosis. One may speak of anesthesia by electrical shock.

The reviewer would like to recall an old electrokinetic hypothesis, namely that protoplasmic streaming is electroendosmotic flow. This had presumably been demonstrated but the experiment was never substantiated. Dubuy & Olson (92) now state that no pronounced difference in the effect on streaming velocity was detected in coleoptiles of wheat when the current flow opposed the inherent electric polarity of the coleoptile, or when it supplemented the inherent polarity.

Protoplasmic movement.—Ameboid movement, the locomotion of flagellate unicellular organisms, protoplasmic streaming, cyclosis, and related phenomena are subjects worthy of a careful and detailed review. As this cannot be adequately done in the space here available, the reader is referred to a recent review covering the whole field (93). Two recent articles will be singled out for consideration.

Without question the most ingenious work done of late on protoplasmic streaming is that of Kamiya (7). He applied air pressure or suction to one half of a strand of slime mold hermetically sealed in a double air chamber. He thus opposed protoplasmic flow. The counter pressure or suction required to stop protoplasmic flow is, when precisely equal and opposite to the flow pressure, a measure of the vital force involved in streaming. From many such measurements Kamiya (94) plotted curves which depict the rhythm of the shuttle or tidal flow of protoplasm in slime molds. The story which these curves tell is an extraordinary one and leads to some profound deductions, among which are that slime mold protoplasm is a polyrhythmic system, that though synchronized to a degree these rhythms exhibit interferences, that these inter-

ferences are beats in the same sense as is sound, and that the rhythm in protoplasm may be subjected to the same exact study as harmonics.

Seifriz & Urbach (95) have distinguished four types of movement in slime molds, namely, growth or increase in mass, streaming or flow within the plasmodium, spreading or displacement of the protoplasm which need not involve progress, and locomotion which is continued progress in one direction involving both streaming and spreading. The most unexpected discovery in their work was that streaming may continue without spread or change in form of the plasmodium; the two have always been considered as inseparable. The authors studied the effects of oxygen and the lack of it, of ethylene and potassium cyanide, and found an increase of two and one-half times in rate of spreading of the slime mold due to ethylene with a sharp maximum at a concentration of 75 per cent. The authors draw a number of conclusions from which the following is one: involved in the total respiratory mechanism is the ability of an organism to apply the last energy reserve still available in any drastic situation to that mechanism which among all the processes necessary for prolonged living is absolutely essential to life.

Chemotaxis.—The movement of organisms toward a source of food, or away from undesirable substances, or toward and away from each other, is an important property of living matter which has been much studied in unicellular forms of life. This movement is known as chemotaxis.

The attraction which eggs have for the sperm of their kind is perhaps the best known example of chemotaxis in life. Also important to mammalian life is the chemotaxis involved in the scavenger duties of leucocytes. Though theories of electrical attraction have been offered in explanation of the migration of white blood cells to the seat of the wound, it is generally agreed that the force responsible is one of chemical attraction.

McCutcheon (96) has discussed chemotaxis from the medical point of view, and Colman (97), with medical applications in mind, studied chemotaxis in the slime molds. Colman applied the reactions of slime molds to the problem of phagocytosis by testing protoplasmic reactions to dextrose, acid, alkali, and sodium chloride. He found a negative chemotaxis of the slime mold *Physarum* for all these substances if above 0.1 *M* concentration. Slime molds or

any motile organism are certain to show negative chemotaxis to any substance if the concentration is high enough. Colman found that slime molds, like leucocytes, are positively chemotactic to dextrose and indifferent to saccharose.

The recurring controversy on how far biological work on lower organisms is applicable to medical work on man, a rather stupid discussion at best, is answered by Colman for at least one situation; he says that there is much similarity in the chemotactic response of slime molds and leucocytes for both are repelled by silicate and both attracted by certain sugars.

A rather special case of chemotaxis is presented by Seifriz (98) who studied the fusion of slime molds and found that on occasion they do not fuse. Having previously observed that the slime mold *Physarum* never recrosses its tracks, Seifriz thought that the failure of some slime molds to fuse when coming into contact with each other might be due to a discarded substance, an exotoxin, which they give off. This substance is to be seen as a colorless slime which myxomycetes leave in their path when advancing. When two plasmodia, or individual slime molds, approach each other they will ordinarily fuse, but occasionally they do not do so. The two plasmodia approach each other and halt at a distance of 0.15 mm. Here they remain, and one may wait in vain for fusion to take place.

The pertinent facts may be stated as follows. When two slime molds rapidly approach each other and meet head-on, fusion always occurs and is immediate, provided the two plasmodia are of the same species and grown under similar conditions. But if the approach is gradual and there is thus time for the waste products of each plasmodium to collect at the approaching surfaces, then no fusion takes place. In short, no plasmodium will enter the zone of toxic waste products surrounding another plasmodium.

Seifriz concludes that exotoxins may be responsible for the failure of some sperm to accomplish the fertilization of eggs of the same species, and the failure of protozoa to conjugate. "Mating types" in *Paramecia* may be determined by the reactions of one type to the exotoxins of the other type. The ingestion of food, the engulfing of living cells by other cells as in phagocytosis, especially the ingestion of some bacteria and not of others by the scavenger cells of the blood may all be examples in which the responsible substance is a cellular exotoxin.

Radiant energy.—The effect of radiation on, and the emanation of energy from living matter are very controversial subjects. It is generally acceded that most forms of radiation affect living matter. Intense light will activate, depress, or kill protoplasm. Nonpulsating extirpated chick hearts may be caused to resume pulsation through stimulation with strong light. The streaming of protoplasm in slime molds is stopped within a few seconds by intense illumination. As radiation effects are dealt with separately in this volume, little should be said here except to point out the need for a far more careful distinction between regions in the electromagnetic spectrum. From a strictly medical viewpoint, it is quite in order to speak of the therapeutic effects of sunlight, without regard for which part of the sun's spectrum is causing the effects for man is subjected to sunlight in its entirety. But a study of the effects of ultraviolet light on protoplasm is almost meaningless unless that part of the ultraviolet spectrum used is specified. Certain regions of the ultraviolet are highly beneficial, others are deadly. The influence of the entire spectrum is the average of these effects. Surprisingly sharp differences have been found by Clough in the reviewer's laboratory (in as yet unpublished work) between very narrow bands in the region just above and below the limit of visibility at the violet end of the spectrum. Protoplasm is killed rapidly above a specific point, and affected but little immediately below this point in the spectrum of an arc light.

It is the lack of careful differentiation between types of radiation and radiation effects which has led many workers to find that the physical-chemical effects on the cell nucleus produced by sunlight, Roentgen rays, ultraviolet rays, and corpuscular Ox- and β-rays are all similar. If radiation of any kind is continued until coagulation and death of the protoplasm occurs, then obviously the results are similar.

Again we have evidence of the applicability of studies on primitive organisms to medicine, and again the medical men give the answer. Warren & Scott (99) have duplicated the earlier work of Seifriz (100) on the effect of radium on slime molds, substituting radon. Their results are very similar to those of Seifriz, namely, the flowing protoplasm of a slime mold slowly approaches a radium or radon needle and halts within a definite distance from it. This distance depends on the strength of the radiation. Seifriz found that plasmodia of slime molds will approach a radium needle and stop within a centimeter of it, then, after a pause, proceed and pass

over the needle, entwining it for a time. The protoplasm cannot however endure the radium emanations indefinitely and therefore soon retreats, only to recover and advance again. Warren & Scott, on the other hand, found that as long as the tube still has a slight amount of radon in it the plasmodium will not grow over it. They also studied the effect of x-rays on the protoplasm of *Physarum* with no satisfactory results. This has been the experience of the reviewer who has several times treated protoplasm with x-rays but each time failed to obtain anything specific other than a general damaging effect to the protoplasm. Warren & Scott conclude from their work that slime mold protoplasm is most sensitive to beta radiation. They had hoped to find a standard, living, test object for emanations. Other forms of emanation, ultraviolet, infrared, x-ray, radium, all will need calibration of their therapeutic value.

Anesthesia.—Anesthesia in itself is hardly to be regarded as a physical property of protoplasm, but the cause, that is to say the mechanism of anesthesia, may involve a physical change in the state of the protoplasm. Seifriz (101) following Claude Bernard believes this to be true. Bernard said that anesthesia is due to the coagulation of protoplasm. This earlier hypothesis met with disfavor, for coagulation is incompatible with life. But since Bernard's day, expressions, and their concepts, such as incipient coagulation, reversible coagulation, and thixotropy (31) have come into use. These phenomena may not differ greatly from gelatinization, long known as the method of setting in gelatin. The mechanism of anesthesia as set forth by Seifriz (101) is one of thixotropic setting or rapid gelatinization of the protoplasm. Whatever one may say of the hypothesis, one cannot deny the experimental evidence. Rapidly flowing protoplasm when subjected to carbon dioxide comes to a stop suddenly through gelatinization and remains in this state until recovery takes place several minutes later.

The chief virtue of a purely physical interpretation of anesthesia lies in the fact that it fits all forms of anesthesia by whatever means produced. This no chemical hypothesis can do. For example, lipoid solubility well explains the anesthetic and destructive effects of fat solvents on protoplasm, but it cannot meet a situation in which a state of anesthesia is brought on by a salt, by carbonic acid, or by shock. An hypothesis which states that the protoplasm of nervous tissue in higher organisms becomes firm or of very high consistency when in a state of anesthesia no matter how produced,

fits all cases of anesthesia whether brought on by ether, magnesium chloride, carbon dioxide, cold, or shock.

That a state of anesthesia should exist when protoplasm has been gelatinized is evident from the fact that with an increase in viscosity there must be a decrease in metabolic activity which reaches a minimum at maximum viscosity or reversible gelatinization of the protoplasm. Lhérisson (102) has pointed out that metabolic rate is inversely proportional to viscosity. He based this conclusion on the fact that the rate of chemical reactions is dependent upon diffusion and rate of diffusion is proportional to viscosity.

An interesting field of speculation is that involving phenomena which border on surgical anesthesia. Unconsciousness brought on by shock, cold, fear, indeed by any means, is in most cases a form of anesthesia; the extremes would be natural sleep and the coma which precedes death. The last may be produced by so simple a means as a sharp drop in blood acidity. Among these exceptional forms of anesthesia that by cold is recognized by the physician. Seifriz & Epstein (103) studied anesthesia by shock. They allowed drops of water to fall from different heights striking slime mold protoplasm. When the drop by its impact stopped protoplasmic flow with subsequent recovery, then from the values of gravity, drop mass, and height from which the drop fell was computed the force necessary to cause anesthesia by mechanical shock. Electrical shock produces similar results.

Still another hypothesis of anesthesia is set forth by Johnson, Brown & Marsland (83). They studied the effects of temperature, pressure, and narcotics on the reversible denaturation reaction of proteins and enzymes involved in the luminescence of bacteria, and conclude that reversible denaturation may be the fundamental basis of narcosis in the living cell.

Rhythm.—All natural phenomena are rhythmic, the movements of the planets, the seasons of the year, the seasonal and life activities of plants and animals, the beat of the heart, and to these may now be added the streaming of protoplasm and the pulsations of a slime mold. Opposition to natural phenomena is an extraordinary one. For example, each new discovery of a rhythm in nature, is likely to be met with the cry of "mysticism." Actually, it is the absence of rhythm which should surprise us. The natural environment of organisms is composed of factors most of which recur rhythmically, heat and cold, rain and drought, short days and long days, cosmic radiation, etc. In such an environment pro-

toplasm would inevitably develop rhythms, in growth, reproduction, metabolism, respiration, and movement. Among the vital activities of protoplasm which are rhythmic are the ebb and flow movement of protoplasm, and the rhythmic pulsation of the plasmodium of myxomycetes. The latter is responsible for the former.

The protoplasm of a slime mold such as *Physarum* flows first in one, outward, direction, and then in the other, inward, direction. If such a plasmodium is photographed on a moving picture film every five seconds and shown at the usual rate of sixteen per second, thus speeding up the apparent rate of movement of the slime mold eighty times, the plasmodium is seen to go through rhythmic contractions and expansions which are synchronized with the outward and inward flow of the protoplasm (23). The mechanism of protoplasmic movement in slime molds is, then, one of rhythmic contraction and relaxation of the plasmodium, with a total of ninety-five seconds for each complete pulsation, forty-five seconds for systole and fifty seconds for diastole; the additional five seconds in time of outward flow accounts for advancement. Kamiya (94) gives 93.7 seconds for one rhythmic period. Three distinct rhythms in slime molds were first revealed in moving pictures (22). Kamiya (94) verified these but added that the protoplasm of slime molds is a polyrhythmic system. Many rhythmic cycles of the motor mechanism are simultaneously operative in one and the same plasmodium.

The outstanding contributions to protoplasmology during the past few years are the general acceptance of the fibrous structural unit and the discarding of the old emulsion hypothesis of protoplasmic structure, the interpretation of protoplasmic qualities such as elasticity, and contractility in terms of the configuration of the folded linear molecule, the fuller awakening to the need of biophysical interpretations of medical problems such as phagocytosis and anesthesia, the placing of the whole concept of the role of electrical forces in animate nature on a sound basis through the measurement of brain potentials which can be correlated with physiological activities, the contributions to the study of protoplasmic movement, and the physical analysis of vital rhythms in terms of harmonics. The last of these contributions is a fine example of the best feature of recent work in biology, namely, the analysis of a biological problem in terms of pure physics, an analysis based on research done with the precision of a physical experiment on sound.

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THE PHYSIOLOGICAL EFFECTS OF RADIANT ENERGY

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Interest in the physiological effects of radiation has been stimulated in the past few years by further advance in our knowledge of ultraviolet radiation (1, 2), by the development of supervoltage x-ray apparatus, and by the invention of the cyclotron with the neutron rays (3) and the large number of temporarily radioactive isotopes provided by it.

It is difficult in a review such as the present to rigidly distinguish between physiological and pathological effects of radiation. Consequently data on some pathological effects will be included when they have definite interest from the physiological standpoint. A comprehensive review of the pathological effects of radiation on normal tissue has been presented by Warren and his associates (4).

Comparative biological efficacy of different types of radiation.— There are three general forms of physical measuring devices in use for determining radiation: (*a*) the ionization chamber with string galvanometer, chiefly used for the measurement of the activity of radium and radon; (*b*) the Victoreen condenser r-meter, chiefly used for measurement of roentgen rays; (*c*) the Geiger-Meuller counter, chiefly used for measurement of radioactive isotopes. Any one of these three measures the ionizing effect of the radiation on air. Although the ionizing effects of different types of radiation may thus be compared, their biological effects are not so readily comparable. Thus a skin erythema may be induced by 300 r at 100 kv. but by 700 r at 200 kv. roentgen rays (5). Dresser reports that 2800 r will not produce an erythema when the rays are generated at 3,000,000 volts by Trump's method. Nevertheless the immediate reactions in the deep tissues are as severe as though produced at lower voltages (6).

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Regardless of the voltage at which the roentgen rays inducing an erythema are produced, the reaction itself will be similar. Thus Stone & Robinson by maintaining biological equivalence between radiation at 200 kv. and 1,000 kv. produced a similar response. About 25 per cent more roentgens were required to produce a comparable dose at 1,000 kv. than at 200 kv. (7).

The ratio of effectiveness of neutrons is considerably greater for a given amount of ionizing effect in air than roentgen radiation, the ratio ranging from 1.8 to 11.8 (3). Variation in biological effectiveness between the different types of radiation varies appreciably with the test object. In preventing regeneration of the forelimb of *Amblyostoma*, neutrons are 13 to 14 times as effective as roentgen radiation (8). Using bean cells as a test object, Gray & Read found neutrons to be approximately 8.5 times as effective as gamma rays (9).

Mottram (10) found the ratio of effectiveness of roentgen and gamma radiation to be 1.3 for the production of cutaneous erythema and 1.5 for the production of epilation and exudation.

Sugiura (11), using mouse sarcoma 180 as a test object, found that 96 r to 114 r produced at 200 kv. were equivalent to the gamma radiation from a gram of radium at 1 cm. distance.

Effects on viruses.—Further work has been done emphasizing the high resistance of viruses to radiation of different types. However, there is appreciable variation in the behavior of different viruses under similar conditions. Thus 10,000 r destroys at least 90 per cent of fibroma virus in rabbit extract, whereas 100,000 r is required to inactivate 50 per cent of the papilloma virus. Interestingly enough the papillomas induced by this highly resistant virus are themselves fairly responsive to radiation, regressing with as little as 5,000 r. This effect is apparently entirely upon the tumor cell, since the same amount of virus can be recovered from the tissues in the region where a papilloma has regressed as can be recovered from a papilloma which has not been irradiated (12).

There is some evidence that irradiation of the host will reduce the natural immunity to the Shope fibroma virus (13).

Effects on bacteria, fungi, algae, and plants.—Recently there has been much interest in the use of small doses of x-ray in the therapy of inflammatory processes of various types. Furunculosis, infectious parotitis, peritonitis, and gas bacillus infection among others have been claimed to have been benefited by relatively small doses

of radiation. An excellent review of the subject by Pendergrass & Hodes (14) summarizes our knowledge at the present time. It is generally agreed that the favorable effect of radiation on inflammation is not due to any direct effect upon the bacteria; they themselves are highly resistant. Dilatation of the capillary and subcapillary network is a fairly uniformly characteristic response to small doses of radiation and it may well be that the active hyperemia thus induced is important in controlling the infection, relieving pain, and promoting elimination of deleterious bacteria products from the local focus. Since small doses of radiation do not affect antibodies and larger doses or repeated small doses do depress the protective mechanisms of the body against infectious processes, it is very unlikely that the good effects noted are brought about by any variation in antibodies. In general the dosages used are too small to destroy leukocytes and to set free enzymes or antibodies from them that might promote the resolution of an inflammatory process, although this latter viewpoint has been suggested by Desjardins (15).

Since root tips and other portions of seedlings have long been used for cytological studies, it is rather natural that they should be utilized for study of radiation as well and much information regarding the biological comparability of radiation has been derived from material of this sort. A consideration of this, however, is somewhat foreign to the present review and will be omitted. However, some points of general physiological interest have been obtained.

A marine vibrio, *Achromobacter*, has been used as a test object by Lorenz & Henshaw to determine the type of x-ray action exerted upon it. When irradiated at 200 kv. roentgen rays, the survival curve is exponential. Hence the organism falls in the "single hit to kill" class (16).

Similar studies on yeast brought out also that *Saccharomyces* belongs in the "single hit to kill" category. The resistance of the organisms was relatively high. Some of the cells lethally affected did not die immediately but underwent several subdivisions following exposure before disintegration (17).

The slime mold *Physarum* is useful in studying early changes induced by radiation. The continual streaming of its protoplasm gives an index of its direction and vigor of growth. The rate and direction of its growth may be altered by beta radiation (18).

Various attempts have been made to modify the sensitivity of

organisms and of dividing cells to radiation. When yeasts are irradiated a higher percentage of cells survive when in oxygen-free air. The presence of oxygen increased the sensitivity to radiation of *Torula*. However, the effects obtained were not constant (19).

Wertz (20) has demonstrated in a detailed study of radiation injury to barley grains that the water content of the grain or root is an important factor and that the greater the water content of the grain, the less radiation is required for injurious effect.

Halberstaedter & Back found an amazing range of sensitivity in a green colonial alga (*Pandorina*). To kill the organism immediately, doses of 300,000 r to 600,000 r were required. While different colonies might vary somewhat in their sensitivity, all the daughter cells of a single colony are killed by approximately the same dose. Although these very heavy doses are required to produce immediate death, delayed death occurring at the time of subsequent mitotic activity may be brought about by doses as low as 3,000 r. Doses under 3,000 r produce no effect either immediate or delayed (21).

An interesting discussion of the effects of radioactive isotopes on plants and animals is presented by Lawrence (22), which includes an autoradiograph of a tomato leaf and stem, which have taken up temporarily a radioactive isotope.

Effects on protozoa and invertebrates.—In a study of the survival curves of the protozoan *Dunaliella*, approximately 18,000 r were required to kill all the organisms using x-ray generated at 52 kv. In samples of the organism exposed a shorter time, giant and odd-shaped forms appeared after a few days. Study of the curves of survival suggested that two different processes were involved; one, an immediate lethal effect, perhaps affecting the cytoplasm of the cell, and the other acting on the nucleus inhibiting reproduction and bringing about delayed death (23).

Paramecium is highly resistant. The lethal dose of roentgen rays produced at 35 kv. lay between 200,000 r and 700,000 r with a half value dose between 300,000 r and 350,000 r. When treated with colchicine for forty-eight hours prior to irradiation to interfere with mitosis, the sensitivity was reduced about one-half (24).

Drosophila eggs make a convenient test object for radiation. The percentage of survival of the eggs (25) is reasonably constant with a given dosage. One hundred to one hundred and fifty eggs in each test lot are usually sufficient to give an accurate result, if the mortality produced lies between 10 and 90 per cent. The pupae of

Drosophila have also been used. They are somewhat more resistant than the eggs to radiation, about 50 per cent being killed with a dose of 2700 r (26).

Pickhan has found that the rate of mutation in *Drosophila* is directly proportional to the amount of radiation. Since the effect is cumulative, the time factor is not important and the process is not reversible. The spontaneous rate of mutation is from 0.3 to 0.6. Radiation with 1,000 r produces 42 per cent mutations (27).

Larvae and pupae of *Aedes aegypti* when irradiated at 35 kv. first increase their activity. When they are irradiated for longer periods of time, their activity diminishes over a period of minutes. When the radiation is interrupted repeatedly at minute intervals, they become inactive during the time they are not irradiated (28).

Henshaw has carried out a series of studies upon the gametes of *Arbacia*. Irradiation of sperm up to 300,000 r or more was required to prevent fertilization of normal eggs. The first cleavage stage was delayed in these eggs fertilized by irradiated sperm (29). This delay in cleavage is chiefly due to a prolongation of prophase in the first cleavage cycle. The entry of the sperm and its fusion with the egg nucleus is not slowed (30). If either gamete is irradiated just prior to fertilization, the cleavage tends to be multipolar (31).

When a homogeneous population of cells is irradiated and the percentage of cells killed is plotted against the dose administered, several types of curves may be produced with different test objects. Henshaw (32) has analyzed the types of response clearly. First, as a single event action: the change produced is the result of a single event, that is, the occurrence of ionization in a region of the cell sufficiently sensitive to cause death. The second type of response is the multiple event type, the effect on the cell becoming apparent only after an accumulation of sublethal events. A third type of response is similar to the second but there may be graded evidence of the effect, that is, a modification of cell activity rather than cell death.

Effects on lower vertebrates.—An ingenious test object proposed by Ellinger (33, 34) is the goldfish. Since water does not vary markedly from the body in its absorption of radiation, determinations of the effectiveness of radiation at different depths in tissue can be fairly well carried out by the familiar water "phantom." Ellinger has greatly improved on this by immobilizing the goldfish at various depths of water and noting the effects of the radiation on the fish.

An interesting relation of environmental radiation is provided by *Salamandra*. A dose of 500 r to 1,000 r to the larvae of *Salamandra* produces no visible skin effect. However, as soon as the larvae leave the water there is evidence of severe skin injury, which leads to death in a short period of time. If the dose is above 600 r, no metamorphosis of the skin occurs, the entire epidermis being discarded and the subcutaneous tissue exposed. The radiation has slowed cell division in the skin, but the effect is not apparent until contact with air necessitates rapid proliferation of the epidermal cells. When the dosage is below 500 r, the skin is thinner, shows fewer glands, and the characteristic spotting does not appear. If the metamorphosis of the larvae is accelerated or delayed, the appearance of the reaction is correspondingly accelerated or delayed (35).

In general lower animals and birds are more resistant to radiation than are mammals although there may be much variation between individual animals of the same species. In the fowl about 2800 r are required to destroy seminiferous epithelium (36).

The chick embryo has been used as a radiation test object and Lea (37) recommends using death two to three days after irradiation as the criterion of effect.

Effects on mammalia.—In a discussion of the response of mammalian cell to ionizing radiation, Failla (38) emphasizes the importance of swelling both of the cells and the nuclei. Anything favoring the imbibition of the fluid enhances the lethal effect of radiation. Wolf (39) noted that marked vacuolization in tumor cell cytoplasm and in nuclei may persist for as long as five months after the cessation of radiation.

There has been some discussion as to whether the roentgen rays act directly or indirectly in producing their effects. An ingenious approach to this problem was made by Barnes & Furth (40), who irradiated one of a pair of parabiotic rats. The roentgen radiation of one rat was followed by pathological change in the lymphoid tissue and bone marrow in the unirradiated member of the pair. This change, however, is slight as compared with the direct effects of radiation. Such effects as appear are probably due to nonspecific factors carried by the circulation.

Osgood (41) has also attempted to answer this question by utilizing the cells of human bone marrow. He irradiated both cells and medium in which they were suspended and found no evidence

of any indirect effect. Such action as was apparent in his experiments was due to direct exposure of the cells to radiation.

Along with the increasing use of therapeutic radiation, there has been much interest in the effects of irradiating externally the entire body. An extensive review by Medinger & Craver (42) presents the therapeutic results obtained in 270 cases of different types of malignant disease by this method. They conclude that the therapy was of most value in the lymphoid diseases. It was their opinion that excessive doses not only injured the normal tissues of the patient but actually made the disease worse. They emphasize the need for following the blood count during the course of treatment to avoid leukopenia, usually the first sign of danger.

The problem of total body radiation comes up not only in connection with therapeutic radiation but also in connection with those occupations bringing persons, such as radium dial workers, radium technicians, and radiologists, into contact with radioactive material. Evans (43) has presented a very clear picture of the dangers involved in these and allied occupations, discussing the matter in detail from the physical standpoint. The proper methods of industrial hygiene to be applied are presented. He establishes tolerance values of 0.1 μg. of radium in the body or 1 micromicrocurie of radon per liter of exhaled breath, and 3 roentgens of gamma radiation per month over the entire body.

A group of cyclotron workers was followed for a number of months by Warren (44). Several received small doses of neutrons inadvertently. None showed permanent ill effects. There was marked variation in the white blood cell counts of individuals exposed to approximately the same amount of radiation.

One way of avoiding the effect of individual variations is suggested by Paterson (45). He suggests that if the average white count of a group of workers exposed to radiation, say radium dial painters, is below 5,000 then it can be assumed that the conditions under which the work is being carried out are unsatisfactory. Similarly if the lymphocyte-polymorphonuclear leukocyte ratio reaches or exceeds 45 to 50, it is fair to assume that the workers are being over-exposed.

Henshaw (46) in a discussion of the tolerance doses of radiation feels that the generally accepted tolerance doses (0.1 r to 0.2 r per day) are safe so far as injury to the skin, to the blood, and the production of sterility are concerned. However, insufficient data have

yet been accumulated to determine whether such a tolerance dose may or may not produce other injuries, such as alteration in germ plasm or the induction of tumors.

Russ (47) states that radon workshops and luminising rooms in England have a radon content of about 10^{-11} curie per liter. If workers in this atmosphere show radon in the breath, due to circulating radon in the blood, it will disappear over the weekend from Friday to Monday. If, however, radon remains in the breath over the weekend, it is due to radioactive material deposited in the body.

A group of radiologists in this country was studied by March (48) and was found to have a tenfold greater incidence of leukemia than physicians not engaged in radiology.

Henshaw (49) has presented a clear summary of the experimental production of leukemia by irradiation. By giving six doses of 200 r monthly to mice, he depressed their leukocyte counts. These slowly returned to and above normal after the treatments were discontinued. A significant number developed leukemia of an undifferentiated cell type.

Changes in blood and in body temperature of guinea pigs as a result of total body irradiation are reported by Bach (50).

The lethal dose for rats when delivered to the entire body is 800 r of filtered radiation both at 100 kv. and 400 kv. (51).

The chemical changes occurring in total body radiation have not as yet been thoroughly studied. Abels (52) and others called attention to fluctuations of the amount of organic acid-soluble phosphorus in red and white blood cells over a period of about twelve days following radiation.

A considerable amount of speculative literature has grown up with regard to radiation sickness. This is at present inconclusive. It has been suggested that vitamin B_1 might be of some value (53, 54) but this has not yet been established. In this regard radon and radioactive phosphorus partly destroy the activity of thiamine chloride while x-ray even in fairly heavy doses had no effect upon it. Heavy radiation of mice produced no alteration in the thiamine content of either the blood or the liver (55).

Steinberg (56) gives criteria for the evaluation of therapy for irradiation sickness and concludes that there is no specific therapy. Although he suggests that the effect may be upon the adrenals, evidence is still lacking as to pathogenesis.

Moon (57) has utilized abdominal radiation of dogs to produce

changes similar to those seen in shock. From 1400 r to 2800 r were given in divided doses. These changes characteristic of shock included visceral congestion, edema of the lungs, and parenchymatous degeneration of liver and kidneys. These alterations were apparently referable to delayed necrosis of the intestinal mucosa as a result of the radiation.

Much of the clinical study of radiation has been concerned with the cutaneous responses. Erythema and swelling have long been recognized as evidence of skin damage induced by radiation. An interesting side light on these cutaneous changes is presented by Pendergrass and others (58), who made counts of the number of open capillaries per unit area of unirradiated and irradiated skin. The per cent of dilated capillaries increased significantly six hours after 300 r generated at 200 kv. were delivered to the skin at 15 cm. target-skin distance. When the distance was decreased to 3 cm., a moderate dilating effect was noted at the end of six hours, which became more marked after twenty-four hours. Changes in function develop more rapidly than this. When localization of trypan blue (59) is taken as an index of capillary permeability, a localization in the rabbit immediately occurs following radiation of the skin with doses ranging from 680 r to 2720 r generated at 86 kv. After three hours the fixation disappeared. Polymorphonuclear leukocytes appeared in the corium after about an hour but there was no correlation between their appearance and the fixation of the dye.

With the interest in wound healing prevalent in recent years, it is natural that the effect of radiation on this should be investigated. A dose of 1800 r, one to three weeks prior to operation, reduced the tensile strength of wounds. A similar dose given twenty-four hours after the operation showed no effect on wound healing (60). In related experiments on rats and dogs, Dobbs found that radiation as much as sixty days preceding operation resulted in some interference with wound healing as evidenced by decreased tensile strength of the wound (61).

In a graphic and beautifully illustrated account, Larkin (62) presents the characteristics of erythematous skin reaction produced by an alpha particle beam from the cyclotron. Subjectively the beam produced a sensation of extreme heat. The exposure lasted about one second. In four hours, the area was erythematous but not painful. The following day it became painful, remaining so for four days. By the tenth day, there was desquamation of the stra-

tum corneum, thickening of the skin, and loss of sensation. On the eleventh day, the region again became erythematous, swollen, and painful, which condition began to regress after eighteen days. However, the thickening and roughening of the skin continued up to four months. The sensation of heat was probably due to stimulation of sensory nerve endings by the radiation. The area received radiation probably equivalent to about 70,000 roentgens.

In a study of the skin reaction produced by neutron radiation, Larkin reported an increased sensitivity of the capillaries in an area of erythema. Histamine injected into the erythematous area produced no wheals but the vessels in the region still responded to vasoconstrictors (63).

It has been suggested by Evans & Kerr (64) that compression of the skin to a sufficient degree to reduce its vascularity will reduce its sensitivity to radiation.

The appearance and method of handling late skin reaction has been adequately covered in the earlier literature on the subject. However, a valuable contribution by Daland (65) emphasizing the danger of infection and of trauma in an irradiated field deserves mention.

Although blood vessels have long been recognized as sensitive to therapeutic radiation, the heart itself is one of the most resistant organs. Leach (66) found no changes in the hearts of animals that had received as much as 7500 r.

In the past few years there has been a considerable revival of interest in the effects of radiation on bone. By means of irradiating the epiphyses in rats, Hinkel (67) has shown that 73 per cent of the growth of the rat femur occurs at the distal end. Young animals are much more sensitive than older and the amount of radiation required to produce minimal stunting bears a linear relationship to age.

While adult hyaline cartilage and fibrocartilage are very resistant to large amounts of radiation, the cartilage columns of the epiphyseal plate can be altered by doses that produce no visible effect on the skin (68). In this study Hinkel gives excellent illustrations of histological detail both shortly after radiation and at later times. He points out that the line of growth arrest produced in the epiphyses by radiation may be similar to that seen in some of the acute diseases of early childhood. The irradiated cartilage cells which grow and migrate distally tend to resume their normal appearance after several months. In young animals, very small doses

of radiation will produce demonstrable histopathological change that returns so entirely to normal that the over-all growth rate will not be influenced.

If the dose is heavy enough to produce changes in blood vessels, osteoblasts, and marrow cells, the effects on cartilage and bone will be more lasting. Large doses in older rats produce abnormalities more slowly but they last longer. In the older animals the dose required to produce change is so heavy that there will be appreciable alteration in the supporting tissues and blood vessels. The degree of modeling of bone and cartilage that takes place proximal to the epiphyseal line is directly proportional to the amount of regeneration of blood vessels and marrow cells. If osteoblasts are absent and the cartilaginous growth has been resumed, a relatively acellular brittle bone-like substance will be laid down. Sometimes as a result of abnormalities induced by radiation at the epiphyses, the cartilage cells may persist and islands of cartilage be found months later incorporated in the new bone.

Barr and his associates (69) in similar studies found that 1800 r produced destruction of cells in the epiphyseal plate of growing rats together with disruption of the cell columns. There was very little evidence of regeneration following this dosage of radiation. In rats ranging from 30 to 180 days old, 1334 r produced a complete arrest of growth and lower doses produced retardation of growth proportionate to the dose. It was of interest that the joints which were treated in the course of irradiating the epiphyses showed no degenerative changes even after nine months.

Following radiation of the femora of young rats, there is a prominent increase in the ash and fat content with a drop in the water content. Some months later, there is a gradual return to normal (70).

Following heavy therapeutic irradiation, partial death of bone in the field of radiation may lead to fracture, spontaneous or following slight trauma. These fractures may be insensitive because of loss of viability of the bone (71).

Ellinger (72) produced a direct effect on the brain cells of goldfish by 100,000 r radiation. Nervous tissue in general is highly resistant. In a study of the mechanism of the relief of pain following radiation, Carty & Bond (73) came to the conclusion that reduction in size of the tumor and effect on blood vessels were probably more important than effect on nerves themselves.

Rat kidney grown *in vitro* is very resistant to radiation.

300,000 r applied for thirty minutes failed to alter either the oxygen up-take or aerobic glycolysis (74).

There have been a number of pathological investigations of radiation pneumonitis during the past few years. Leach (75) has found that with radiation pneumonitis there is a marked lowering of the vital capacity. This reduction is due not only to intrapulmonary changes but also to changes in the thoracic wall leading to abnormal respiratory function.

The radiation of male mice with doses ranging from 600 r to 800 r leads to an interesting hereditary change. The animals remain fertile for about two weeks following radiation, then are sterile for a period of three months, and then show a partial or complete return of fertility. The partial loss of fertility is due to chromosomal mutations. When these mice are mated with normal females, half the offspring are normal in appearance but are semifertile (76).

Patients receiving local x-ray therapy for neoplastic disease of one or another type have been studied to determine the types of systemic change that might be induced. Goldman (77) followed a group who had been treated with 200 kv. roentgen rays over fields of varying size but stopping well short of total body radiation. He found the excretion of total nitrogen to rise due in part at least to the destruction of masses of tumor tissue. There was also some increase in uric acid excretion, which suggested an increased endogenous tissue metabolism. The metabolic rate, however, did not vary significantly. Those patients that suffered from radiation sickness showed low chlorides probably due to vomiting. There were no specific changes which consistently appeared in the patients. Robertson (78) working in the same institution as Goldman followed a group of seven patients treated with 1,000 kv. roentgen rays. He found no significant difference in metabolic changes between this group of patients and those that had been irradiated at 200 kv.

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PHYSIOLOGICAL ASPECTS OF GENETICS

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It is appropriate to begin this review by calling attention to the posthumous appearance of "The mutants of *Drosophila melanogaster*" by C. B. Bridges, completed and edited by Katherine S. Brehme (1). While not explicitly physiological, the type of work of which this monograph is the culmination underlies all physiological genetics and is of the greatest significance in its implications.

Multiple alleles.—Inspection of the descriptions of the *Drosophila* mutations brings out well the justification for the conventional concept of the gene, as a first approximation. Multiple alleles are known at a large proportion of the loci. Allelic mutations are usually much alike, differing mainly in degree of divergence from type. Dominance is usually correlated with order of effect and the compounds of two recessive alleles are usually intermediate. In contrast, there is little or no tendency toward resemblance in the effects of neighboring nonallelic mutations. There are, however, interesting exceptions to these rules, some of which are being studied intensively for their implications with respect to the nature and physiology of the gene.

Stern (2) and Stern & Schaeffer (3) have made such a study of certain cubitus interruptus alleles and find that two independent variables are required to account for effects on even a single criterion, venation. They postulate that all of the alleles control the transformation of a single substrate into a single product, but analyze this into two steps in which alleles may differ independently: power of combining with substrate, and rate of formation of the product. The reaction must be noncatalytic to permit independence, since if the ratio of gene (or gene controlled agent) to total amount of substrate is small, there can be no effective differences in competitive power. Under the otherwise less plausible hypothesis that a common substrate may be transformed into somewhat different immediate products with different efficiencies relative to the observed character, substrate transforming power and product efficiency may be quite independent even with catalytic action (4). With a single immediate product of all alleles, effects on different characters should be parallel (except for thresholds). This is not

necessary if there are different immediate products. It turns out that there is no parallellism in the effects of the *ci*-alleles on venation, crippling of the legs, and tendency to extra bristles.

Other exceptional cases can be accounted for by postulating that alleles may differ with respect to which of a group of related substrates they are able to transform. If the products affect the same observed character, completely recessive alleles may have the same or similar effects and yet reconstitute the dominant type in their compound as in several cases in *Drosophila melanogaster* (1).

Whiting (5) suggests that sex determination in *Habrobracon* (and probably other hymenoptera) may rest on a mechanism which may be interpreted as of this sort. He has demonstrated a series of at least nine alleles. The ordinary haploid males may carry any one of these, yet are alike phenotypically. Homozygous diploids of all sorts are also males, indistingushable from each other, while all kinds of heterozygotes are phenotypically similar females. Whiting postulates a chromosome segment within which crossing over does not occur and which contains numerous sex genes. The various "alleles" are held to consist of different combinations of dominants and recessives with consequent complementary effects in heterozygotes. This general scheme may be illustrated by postulating that each "allele" has one positive component ($A_1a_2a_3$—A_9 $a_1A_2a_3$—A_9 etc.), that each positive component acts on a somewhat different substrate which is sufficiently limited in amount to permit dominance, and that all of the products are equivalent in switching sex differentiation. In haploids and homozygotes the ratio of A components to other genes would always be 1 to 1; in heterozygotes, always 2 to 1, giving a mechanism of sex determination analogous to that familiar in other animals. There is, however, the alternative view that femaleness may be attributed to a reaction to the introduction into the egg of a foreign antigen.

More generally, there may be two or more substrates which multiple alleles act upon with different relative efficiencies. Here there would be competition of two substrates for the same gene as postulated for the C series in guinea pigs (4). There may also be partially complementary effects as in the brachyury series of the mouse, discussed later (6). Oliver & Green (7) find such a situation in effects of lozenge alleles of *Drosophila* on viability and fertility. Jones (8) finds that mutations that arise from time to time in long

selfed lines of corn tend to have a complementary effect (heterosis) when crossed to the parent type as if the mutant acted more efficiently than the latter in some respects but less efficiently in others. Stadler & Fogel (9, 10) and Silow & Yu (11) describe partially complementary effects in extensive series of multiple alleles affecting color in corn and cotton respectively.

The difficulty indicated above in making a sharp theoretical distinction between allelism and complete linkage in certain cases has been enhanced by the discovery of cases in which rare crossing over occurs between genes that would otherwise be considered as alleles because of the type of interaction in compounds (7, 12). It seems probable that there may be longitudinal replications of pattern within the gene and that these tend to drift apart in physiological properties, under a well known evolutionary mechanism, ultimately becoming separate genes subject to crossing over and complete separation by chromosome breakage and rearrangement. It does not appear practicable to limit the term gene to ultimate self-duplicating entities (if these are distinguishable at all). Practically the boundaries of the gene become a matter of convenience: a block of self-duplicating material of a chromosome which is not subject to crossing over or chromosome breakage.

Position effect.—Position effect has long been recognized as a phenomenon which should throw light on immediate gene physiology. Stern & Heidenthal (13) have obtained results in *Drosophila melanogaster* that pose a problem for any theory. They used translocations R(ci) between chromosomes III and IV, involving cubitus interruptus and between chromosomes I and IV, involving a dominant type allele R(+). Genotype R(+)/ci had interrupted veins (reduced dominance of type) confirming Dubinin & Siderov who also had found R(+)/R(+) and Haplo R(+) to be normal. Genotype +/R(ci) also had interrupted veins and ci/R(ci) was more extreme than ci/ci. The authors give alternative interpretations of these results but note the difficulty of fitting these to another observation, that R(+)/R(ci) is usually normal.

Ephrussi & Sutton (14) discuss the difficulties with the usual interpretations of position effect, and suggest that it is a result of stress near the affected loci due to changed conditions of pairing of homologs. The obvious difficulty with this hypothesis in cases of position effect in homozygotes and hemizygotes they account for as due to stress resulting from the tendency toward nonhomologous

pairing of heterochromatin, thus bringing in the well known relation between position effect and proximity to heterochromatin. As they note, however, the disappearance of position effect in heterozygotes between different translocations, illustrated above, is not easily accounted for.

Sutton has published instructive analyses of position effects at the Bar locus and of relations between breaks and phenotypes in the yellow-scute region of *Drosophila melanogaster* (15, 16). Roberts (17) gives an exhaustive statistical analysis of the characteristics of thirteen reciprocal translocations in corn for possible position effect. There were slight differences from type in both heterozygotes and homozygotes.

The nature of the difference between heterochromatin and euchromatin continues to attract attention (18, 19, 20). The idea has been developed that heterochromatin consists of regions in which the same gene is duplicated many times. This is correlated with the idea that it consists of genes which have to do with mass products (nucleic acid, tissue protein), in contrast with ones concerned with products such as enzymes required only in small amount. It has also been associated with multiple factor heredity (21) although it should be noted that the latter requires similar effects in different chromosomes (or at least in widely separated loci) rather than duplications in one region.

There is, however, some question of the criteria for heterochromatin. Muller (22) distinguishes between "'blocks" which make up a large portion of the length of the mitotic X-chromosome of *Drosophila melanogaster* but relatively very little in the much larger salivary chromosomes, and the residual heterochromatin. He finds the former virtually unbreakable under x-ray treatment, the latter much more breakable than euchromatin.

Chromosome chemistry.—Mirsky & Pollister (23, 24) have described methods of extracting a nucleoprotein, consisting of highly polymerized pure desoxyribose nucleic acid in loose combination with basic protein, which is wholly protamine in nucleoprotein from mature sperm of trout, but wholly histone in that from blood cells and liver cells. The yields are roughly proportional to size of nucleus and range upward to 90 per cent of the dry weight in the case of trout sperm suspensions. Mechanically isolated chromatin threads assayed nearly 100 per cent nucleoprotein. Claude & Potter (25) describe similar results for rat leukemic cells.

Stedman & Stedman (26) report results that seem to be in serious disagreement with this account. They find an acid protein more complex in amino acid content than histone and protamine, as a major constituent of cell nuclei, including those of fish sperm. According to them, this protein which they call chromosomin, is responsible for the characteristic staining reactions of nuclei. They estimate cod sperm to contain 28 per cent nucleic acid, 12 per cent histone, and 60 per cent chromosomin.

Schultz & Jose (27) note differential staining reactions of the bands and interbands of *Drosophila* salivary chromosomes which must be attributed to protein differences rather than to the differences in nucleic acid content.

The most suggestive recent result bearing on gene chemistry comes from work on bacteria, which have no clearly recognizable chromosomes. Type specificity in pneumococcus depends on a polysaccharide capsule with very strong antigenic properties. It was shown many years ago that specificity could be removed (e.g., by treatment with antiserum), giving "rough" unencapsulated strains, with a tendency to relapse to capsule production, always of the original specificity. Means of transforming type by use of extracts from dead bacteria of the desired type were, however, discovered. Avery, MacLeod & McCarty (28) have now obtained the active principle of such extracts in apparently pure form by fractionation methods. It turns out to be a polymerized desoxyribose nucleic acid, molecular weight about 500,000, lacking type specific carbohydrate and protein as indicated by very sensitive serological tests. Yet it can induce an unencapsulated pneumococcus derived from one type to produce thereafter the specific carbohydrate of the type from which the nucleic acid has been derived as well as more nucleic acid with this property. The great possible significance of this observation in the interpretation of the role of the nucleic acids of chromosomes and of other self-duplicating entities is obvious.

Induction of mutation.—We may note first a paper by McClintock (29) on the systematic production of small, haplo-viable deficiencies in corn by providing the conditions for mechanical breakage (chromosome bridge and breakage-fusion cycle).

The induction of gene mutations by ionizing radiation has been variously attributed to the direct effects of single ionizations or activations, effects of clusters, and indirect effects, more or less

remote from the site of the "hit." Zimmer & Timofeeff-Ressovsky (30) present additional data from the use of x-rays and neutrons on *Drosophila* from which they conclude that ion clusters may be excluded as the primary events (frequency of these per unit dose increases 30 per cent in the range from 10 kv. x-rays to γ-rays while mutation rate is constant). Fano (31) in a theoretical discussion concludes that this independence of wave length does not warrant the conclusion that mutation is a direct and invariable consequence of a hit within a postulated definite sensitive volume of a gene. Giles (32) and Fano (33) add corroboratory data for the conclusion that neutrons are only about half as effective as x-rays per unit of energy absorption in inducing recessive lethals in *Drosophila*. This favors the view that the diffusion of effects is at least not so great as to prevent wastage of ionizations in the dense ionization tracks found with neutron bombardment.

Giles (32) also adds to the data indicating that neutrons are considerably more effective than x-rays in breaking *Tradescantia* chromosomes and that the frequency of all types of rearrangement rise only linearly with dosage. Fano (33) finds the same for breakage of *Drosophila* chromosomes. Similar results are also found for dominant lethals by Demerec & Fano (34) who note that this is in harmony with Pontecorvo's suggestion that these are largely isochromatid rejoins. The rise of gross aberrations linearly with dosage and absence of any differential effects of duration or intermittency of treatment in the case of neutrons (32), contrast with the results of x-ray treatment (35) under which gross aberrations increase as the square of the dosage if duration of treatment is constant, but less rapidly under other conditions, in such a way as to indicate rapid loss of capacity of broken chromosome ends to rejoin. The new results thus strengthen Giles' hypothesis that it requires a cluster of ionizations to break a *Tradescantia* chromosome and that most double breaks under neutron treatment are due to single ionization tracks. Lea & Catcheside (36) present a thoroughgoing attempt to reach a quantitative theory for breakage of *Tradescantia* chromosomes. They estimate the mean period of "healing" of broken chromosome ends to be about three and a half minutes. They are led to the conclusion that the chromosome must be traversed by about seventeen ionizations in order to break. An isochromatid break requires traversal of both chromatids by a single track. Traversal of separate chromatids which may

be up to 1 or 2 μ apart, by the same track should theoretically be the most frequent cause of gross aberrations, which would account for the linear relation to dosage. Their hypothesis that traversal by any proton track should result in a break is not, however, in harmony with an observation of Giles (32) that neutrons with energies up to only 7.5 mev are more efficient than ones with energies up to 15 mev and thus with less dense tracks.

In the case of x-radiation, Lea & Catcheside estimate that wave length 4.4 Å should be most efficient in producing the requisite number of ionizations in a path of sufficient length to traverse a *Tradescantia* chromosome. Efficiency should fall off rapidly with greater wave length, becoming almost nil at 6.4 Å (too short a track) and should also fall off with wave lengths less than 4.4 Å because of insufficient density of ionization in all but the tail of the path of the secondary electron. Efficiency should not change much below 2 Å, however, because of probable approximate constancy per unit dose of tertiary clusters of requisite size. In a later paper (37) they confirm these predictions, obtaining maximum chromatid and isochromatid breakage at 4.1 Å, less at 1.5 Å and 0.15 Å, and least at 8.3 Å.

Koller & Abend (38) find no single breaks and a deficiency of odd numbered breaks in x-rayed sperm of *Drosophila*. Kaufmann (39) describes a larval female *Drosophila* (father x-rayed) with at least 32 breaks detectable in the salivary chromosomes. Fano (40) discusses the mechanics of induction of gross rearrangements in *Drosophila* sperm. He stresses the effects of one union on others, after union begins following fertilization. McClintock (41) describes a case in which there was union in the zygote of ends of chromosomes broken in the male and female gametophytes respectively. Sax (42) finds that centrifugation during x-radiation of *Tradescantia* microspores increases the frequency of aberrations. Colchicine treatment prior to x-radiation on the other hand was found by Brumfield (43) to cut down the rate of chromatid aberration.

While evidence is accumulating that chromosome breakage by ionizing agents requires a cluster of ionizations, it is also clear that it can occur under ultraviolet treatment, without ionization. The mechanisms however are clearly different. Ultraviolet produces only single deletions to an appreciable extent, while x-rays produce all types. Swanson (44) confirms these conclusions and

finds that treatment of pollen tube nuclei of *Tradescantia* by ultraviolet tends to inhibit the production of aberrations by x-rays an hour later. Treatment by ultraviolet an hour after x-radiation inhibits single deletions. It is suggested that ultraviolet has an effect on the matrix favoring restitution. Kaufmann & Hollaender (45) find that ultraviolet, and also near infrared, following x-radiation of male *Drosophilas*, reduces aberration rate.

The evidence from various organisms that the most effective wave length of ultraviolet in inducing mutations is about 2650 Å (where the strong absorption band of nucleic acid is located) is extended by experiments on spores of *Penicillium notatum* (46).

Gene *a* of corn (colorless aleurone) is ordinarily a stable recessive. In the presence of Dt it mutates freely to a dominant allele, *A*. Stadler (47) finds that x-rays produce no mutations of *a* (in *aa dt dt*) with doses capable of yielding about 900,000 losses or inactivations of *A*.

Mampell (48) describes a gene in *Drosophila pseudoobscura* that causes a general increase in mutation rate, 35-fold when heterozygous, twice this when homozygous.

Such genes as these presumably act through chemical channels. Direct attempts at inducing mutations by chemical treatment continue largely disappointing. Treatment of eggs or larvae of *Drosophila melanogaster* with deuterium (49) and with proteolytic enzymes (50) gave no detectable increase in lethal mutations. A study of the effect of copper sulphate and high pH on the rate of mutation of the unstable gene mt-3c of *Drosophila virilis* gave an effect but in the direction of decrease (51).

Mutations in unicellular organisms are attracting increased attention. Luria & Delbrück (52) find that the statistics of occurrence of resistant clones of colon bacteria on treatment with a bacteriophage indicate chance mutation (rate 0.32×10^{-8} per bacterium per division cycle) rather than a directed response. Spiegelman, Lindegren & Hedgecock (53) have studied adaptive fermentation of galactose by yeasts. A technique for observation of individual cells revealed that in a nonadapted haploid strain adaptation was a matter of individual mutation. A culture became adaptive only by selection in an increasing population. But in a particular diploid strain, 100 per cent adaptation occurred abruptly without cell multiplication after a lag of three hours. Other diploid strains did not develop adaptive enzymes.

Sturtevant (54) discusses the likelihood of specific induction of mutations by serological methods in view of the direct relations between gene and antigen. Emerson (55) describes tests of this hypothesis with *Neurospora*. Antisera produced 25 variants in 695 treated lines (0 in 276 controls) of which at least 11 were found to be simple Mendelian. The evidence indicated induction rather than selection.

Transformation from one type of pneumococcus to another by means of extracts from the latter has already been discussed (28). The results suggest chemical isolation and transfer of a gene rather than induction of mutation.

Genes and antigens.—The likelihood that the specificity of antigens reflects that of genes more directly than does any other character makes progress in this field of special interest in physiological genetics. The Rh series of antigens of human red blood cells has been the object of intensive study recently. One pair of alleles (Rh, rh), independent of those responsible for the A, B, O, and M, N antigens is indicated where the criterion is agglutination by a particular antiserum (56). By testing each individual of a family with several different antisera, however, there is evidence for at least six alleles (57, 58). Each of three of these, Rh_0, Rh′, Rh″ [Wiener's revised terminology (59)], determines a distinct specificity. Two others, Rh_0' and Rh_0'', combine the specificities indicated by subscript and superscript while rh was not responsible for any positive reaction to the test sera. Heterozygotes exhibit all of the positive effects of the two genes. Other sera have been obtained which reveal agglutinins determined by some at least of the class of alleles called rh (60, 61).

The number of antigens found in the red blood cells of cattle has reached about 40, according to Stormont, Irwin & Owen (62). Here as in man there is evidence for multiple alleles with compound specificities.

Irwin & Cumley (63) have continued their studies of the genetics of antigens in the red blood cells and serum proteins of numerous species of pigeons and doves and their hybrids, bred by Cole. The common and specific cellular antigens of eleven species of *Columba* form an interlocking pattern with only slight group differentiation of old and new world species (64, 65). A study of the serum antigens of the Senegal dove, absent in the Ring dove, was carried to the fourth back cross to the latter (66). Segregation of

at least three (probably four) independent antigens was established. These were independent of the ten cellular antigens differentiating Senegal from Ring dove. It is noted briefly that pigeon-dove crosses gave results that indicated intraspecific as well as interspecific differences in genes determining serum antigens. Two species of duck, the Mallard and Muscovy, are found to have specific as well as common red blood cell antigens [McGibbon (67)]. Their sterile F_1 hybrid has most of the parental antigens but also a new hybrid antigen, analogous to those of certain Columbid hybrids. A Muscovy male proved to be heterozygous for two alternative antigens both absent in the Mallard.

It has long been established that a hostile reaction to a transplanted tissue usually depends on the presence in the latter of dominant genes, presumably determining antigenic specificities, that are not present in the host. Specificity genes of the host, absent in the graft, are of little or no significance. Results of transplants within and between two distinct inbred strains of rats, previously reported by Loeb & King, could only be reconciled with this theory on the hypothesis that these strains had remained heterozygous in spite of 67 generations of brother-sister mating. Data from generations 91 to 106 now show an approach to the expected tolerance of transplants within strains, with lack of tolerance between (68). But unexpected tolerance of grafts from individuals derived from a recent cross between the two lines raises a new difficulty.

Self incompatibility in plants is probably related to these specificity reactions. Most cases involve only one locus with numerous alleles. There is inadequate growth of pollen with an allele present in the style. The great number of such alleles at one locus is illustrated by recent studies of Atwood on white clover (69). In one small highly isolated population 36 of 49 tested alleles proved distinct. In another larger isolate, 39 of 49 were distinct.

Tetraploids from self sterile diploids behave differently in different cases. Homozygous pollen (e.g., S_1S_1) seems always to be inhibited by presence of the same gene in the style, but with heterozygous pollen (e.g., S_1S_2) the inhibition tends to be reduced to varying extents. In *Oenothera organensis* (self sterile) the tetraploids are still self sterile but the growth of heterozygous pollen tubes, especially of certain genotypes, is much greater than that of homozygous pollen tubes (70). In *Oenothera rhombipetala* pollen is also successful only if both its S-genes are foreign to the style

(71). Tetraploids from self sterile pears on the other hand are self fertile. Heat shock of the pollen mother cells of diploids, followed by selfing, results in triploid fertile seeds (72). Atwood (73), working with white clover, finds a more complicated situation. Two tetraploids were self sterile but crosses between them yielded 26 self compatible to only 3 self sterile clones. Practically all possible tests of cross pollination between these clones were made and gave results which the author interprets on the hypothesis that the presence of two or more kinds of heterozygous pollen (possible in trialleles such as $S_1S_1S_2S_3$ and tetraalleles $S_1S_2S_3S_4$) favors pollen tube growth, which thus is assumed to depend on the reaction between stigma and all of the pollen placed on it. There are, however, as he notes, serious discrepancies under this hypothesis. The results can be explained qualitatively better by the hypothesis of Lewis (70) that there are great differences between the reactions of different kinds of heterozygous pollen tubes in seemingly similar situations.

The phenomena associated with mating types in ciliate protozoa appear somewhat similar to those of self sterility in plants (74). In *Paramecium*, conjugation ordinarily occurs only between different mating types of the same species and variety. Mendelian segregation occurs but the phenomena are complex. There is a very different situation in *Euplotes patella*. Kimball (75) finds six types based on the possible combinations of three alleles, mt^1, mt^2, and mt^3. Each gene, acting independently in heterozygotes, appears to be responsible for secretion of a specific substance which induces conjugation in any genotype which lacks the corresponding gene. Thus fluid from heterozygotes induces conjugation within clones of the five other types while fluid from homozygotes does this for only three of them. Powers (76) finds that mating type in clones of double animals is determined by the independent action of the genes of both nuclei, which may be different.

In higher animals a rather high degree of self sterility is found in tunicates. Morgan (77) presents data bearing on the genetics and physiology. The block is in the egg membrane (a diploid product) and can be overcome by rupture or treatment with acid. There is clearly a genic basis but the phenomena are complex. It is held by the author that cross sterility, exceedingly rare between random individuals and not very frequent even among progeny of one individual, depends on close similarity (demonstrably not always

identity) with respect to genes in several extensive multiple allelic series. The natural self fertility (of about 5 per cent of wild individuals) is attributed to differences in the germ tract due to mutable genes. One-way cross sterility is commoner than reciprocal. This is easily explained, as noted, if sperm specificity is under control of the haploid nucleus, but no other case of action of the sperm nucleus is known. If under diploid control, it calls to mind the asymmetry in human blood group reactions.

Genic control of metabolic processes.—Rapid progress has been made in the analysis of genic control of metabolic processes of the mold, *Neurospora*, by Beadle, Tatum, and associates (78). This organism is admirably adapted to determination of genes and their relations by the possibility of growing separately all of the products of the reduction division (ascospores from the same ascus) following a cross.

Type *Neurospora* can be grown on a medium containing no other nutrients than inorganic salts, a simple sugar, and biotin (79). In these experiments (78), perithecia or conidia are treated with x-rays or ultraviolet light to induce mutations. Single spore cultures are then grown on a medium designed to supply any necessary diffusible substance which a mutant may have lost the capacity to synthesize. Normal growth on this medium, but failure of subcultures on the basic medium, indicate such a mutation. Trials with progressively simpler supplements to the basic medium have usually led to the discovery of a single substance (or any one of a group of closely related substances) as all that is needed as a supplement to restore full growth. Among such substances, each effective with a particular mutation, are several amino acids (78, 80, 81), e.g., arginine, methionine, tryptophane, lysine, valine, leucine; several vitamins (78, 82), e.g., thiamine, nicotinic acid, pantothenic acid, *p*-aminobenzoic acid, pyridoxine, choline; and pyrimidine nucleosides, uridine or cytidine (83). There have often been recurrences of what appear to be exactly the same mutation. In several cases, however, what at first appears to be a recurrence has turned out to involve inactivation of a different link in the chain of processes leading to the supplement in question. Thus one mutant will grow if either thiamine or thiazole is added to the basic medium. Another will grow on addition of thiamine but not with either thiazole or the pyrimidine constituent as the supplement (78). The interpretation is that a step in the synthesis of

thiazole fails in the former, the final step in the synthesis of thiamine from its constituents in the latter. Similarly (78) one "methonineless" mutation can utilize homocystine or cystine as well as methionine, while another cannot add the methyl group to homocystine to produce methionine. The "tryptophaneless" mutations (84) can utilize indole [to combine with serine to form tryptophane (85)] as well as tryptophane itself but one type can also utilize *o*-aminobenzoic acid while another cannot.

The most extensive chain analyzed concerns fifteen mutations which grow normally with arginine as the sole supplement (86). Four nonallelic members of this group also grow normally with either ornithine or citrulline as the supplement. Presumably these determine four different steps in the synthesis of ornithine. Two nonallelic mutations which can utilize either citrulline or arginine but not ornithine presumably control two different steps in the synthesis of citrulline from ornithine (which involves taking up of ammonia and carbon dioxide with loss of water). One type of mutation can utilize only arginine, which is derived from citrulline by taking up of another molecule of ammonia (with loss of water). Other mutations appear to be exact recurrences. Finally, arginine can be hydrolyzed into ornithine and urea (87), as in the ornithine cycle of mammals.

It is possible to study dominance in spite of the haploid state of the nuclei, by allowing the syncytial hyphae from two mutations to fuse to form a heterocaryon in which the nuclei from the two sources freely intermingle (88). In most cases, each kind of nucleus is able to carry through the metabolic steps in which the other fails to a sufficient extent to permit normal growth. There is often indeed a wide factor of safety. Thus tests indicated that the ratio of "pantothenicless" to "nicotinicless" nuclei might vary between 1 to 3 and 5 to 1 without disturbance of normal growth. On the other hand, certain morphological mutants that by themselves grew only about 1 per cent as rapidly as wild type gave heterocaryons that still grew only about half as rapidly as wild type, a fact indicating that there is no ratio of nuclei attainable by natural selection, in which both nuclei are adequate. Such mutations may be considered semidominant.

A physiological test for identity (or at least allelism) of two apparently similar mutants can be made by forming a heterocaryon and determining whether there is complementary action.

Thus two kinds of "nicotinicless" complement each other (88).

A substance that improves growth is not necessarily one whose synthesis is interfered with in the mutant in question. Thus a mutant "cholineless" grows normally from the first with choline (or lecithine) as supplement (89). There is some growth however with the unrelated substance methionine (in relatively large amounts) as the only supplement and much improvement if this is added to inadequate amounts of choline. These results are interpreted on the hypothesis that the mutation blocks only the synthesis of choline but that one of the uses of choline (probably that of supplying methyl groups) is relieved by addition of an excess of methionine.

In some cases it has not been possible to alleviate the metabolic defect due to a mutation by any single substance. Thus one mutation grew normally with a mixture of 70 to 80 parts of valine, 30 to 20 parts of isoleucine, but hardly at all (at first) with less than 5 per cent or more than 70 per cent isoleucine in the mixture (80). Either of these amino acids but not both could be replaced by their keto-acid analogs. Neither of the hydroxy-acid analogs were effective. Yet leucine or either its keto- or hydroxy-acid analog could largely replace the valine. Certain amino acids (phenylalanine, norleucine, and norvaline) were strongly inhibitory. Presumably one link in a network of processes is blocked but no simple interpretation has been found.

In this case and in certain simpler ones, a mutant that grew hardly at all at first on the basic medium gradually acquired the capacity to grow at a normal or nearly normal rate. The adaptation is not transmitted to the conidia.

An interesting application of these results has been in the bioassay of certain substances: *p*-aminobenzoic acid (79), choline (89), and leucine (90).

Isolated examples of genic control of simple metabolic processes, in some cases associated with presence or absence of demonstrable enzymes, have been described in other organisms. Sawin & Glick (91) find that the blood of some, but not all, rabbits contains an enzyme capable of destroying atropine and related substances. The presence of this atropinesterase was demonstrated to depend on an incompletely dominant gene. Corkill (92) and Atwood & Sullivan (93) agree on two independent genes as concerned in the production of cyanide by white clover. One dominant gene

determines the presence of cyanogenic glucosides (lotaustraline, linomarine) while another dominant gene determines the presence of a hydrolytic enzyme, linamarase.

In other one-factor cases, the metabolic effect is less easily located. Thus Weiss (94) finds a one-factor difference in soy beans between strains that are normal (dominant) and ones that are chlorotic on calcareous soils. In nutrient solutions, the recessives become chlorotic when the concentration of available iron is low. Their tissues showed relatively high pH, low potassium concentration, high total iron content, but low soluble iron.

In other cases, metabolic differences are due to multiple factors. An example is percentage of sucrose in sugar beets which gives multiple factor heredity with no evidence of a matroclinous tendency after crosses (95, 96).

Ephrussi has reviewed the extensive studies on the relations of genes to the physiology (97) and chemistry (98) of eye pigments of *Drosophila*. This work has related largely to effects on diffusible substances. Ephrussi & Herold (99) describe techniques for the extraction and quantitative estimation of the red and yellow pigments as a basis for the study of the effects of the eye color genes which have not been adequately attacked by the earlier methods. Caspari (100) finds a higher tryptophane content in recessive red eyed *Ephestia kühniella* (aa) than in the dominant black eyed form (a^+). Other evidence indicates that tryptophane is a precursor of the diffusible a^+ substance which in turn is a precursor of the pigment. In another paper (101) he describes a new gene which affects testis color autonomously in contrast with the nonautonomous effect of a^+ on testis as well as eye pigment. Brehme & Demerec (102) give a survey of the effects of the eye color genes on testis color in *Drosophila melanogaster*. There are interesting cases of nonparallelism even within the same series of alleles.

Attention may be called to recent reviews on the embryology of vertebrate pigment cells by DuShane (103, 104) as furnishing a background for interpretation of genetic data on pigmentation. Willier & Rawles (105) describe experiments in which melanophores from cross bred fowl embryos (Rhode Island Red ♂ × Barred Plymouth Rock ♀, the latter with dominant sex-linked genes for barring and silver and an autosomal dominant for black, all lacking in the former) were grafted on White Leghorn embryos. The melanophores of males (barred) and of females (black-red

stippled) both developed autonomously in host feathers irrespective of the sex of the host. The relative frequency of differentiation of female melanophores into black and red pigment cells was found to depend partly on genic modifiers in the donor and partly on the physiological properties of individual feather germs of the host (position in the regional gradient, growth rate, etc.). The barred pattern given by the male grafts was also affected by the properties of the host feather germs. It is noted that differences in the form and size of the black and red granules indicate two directions of differentiation rather than a sequence, arrested in one case. Nickerson (106) describes the results from grafts characterized by two different kinds of barring: sex linked barring of Plymouth Rocks in which the pattern has a period of five or six days, and autosomal barring of Silver Campines in which the period is only about half as long. Both rhythms were maintained in the feathers of White Leghorn hosts, a fact indicating that the periodicity is intrinsic in the melanophores. The melanophores in a given feather obviously do not, however, act independently of each other. It appears probable that regulation occurs through diffusible inhibitory substances produced by the melanophores.

Light is thrown on the immediate cause of differentiation into black and red melanophores by experiments by Wang (107). He finds that autotransplants of whole feather papillae (dermis plus epidermis) from one tract to another produce feathers of the same type and pigmentation as if left undisturbed. Transplants from papillae in which the epidermis has been destroyed produce feathers of the type and pigmentation of the host tract (which furnishes new epidermis to the papilla). The dermal component is necessary as the inductor of the feather and determines its orientation but type and pigment differentiation depend on tract specificity of the epidermis. Foulks (108) has shown that melanophores do not maintain themselves in the papilla but must be continually supplied from the subepidermis. Wang's results thus seem to require that they are not differentiated as to tract until coming under the influence of the epidermal component of the papilla. Transplantation of papillae between breeds (109) invariably yielded feathers of host tract specificity and pigmentation. The epidermal component of the papilla is believed to be wholly lost as a result of breed incompatibility. The melanophores must trace to the host

subepidermis rather than to the grafted dermal papilla in agreement with Foulks' observations.

The effects of various genotypes of the mouse on size, shape, color, and abundance of pigment granules is described briefly by Russell & Russell (110). Harmon & Case (111) describe the effects of several genotypes of the guinea pig on eye pigmentation. Bohren *et al.* (112) give histologic and photometric comparisons of various pigments of the fowl. Baker & Andrews (113), and Ginsburg (114) give photometric comparisons of black and yellow in the guinea pig. It is agreed that the absorption curve for yellow is steeper than that for black in both fowl and guinea pig but whether this implies a chemical difference or merely a difference in colloidal state is not clear.

Ginsburg (114) describes the effects of colorless extracts obtained from the skins of young guinea pigs of diverse genotypes in producing artificial melanin from dopa. An inhibitor was easily demonstrated especially in extracts from white skin (whether of albinos or spotted). This was removable by scraping the skin and thus appeared to be in the epidermis. The extracts from certain genotypes contained an active principle probably a polyphenol oxidase. The potency of extracts from different phenotypes depended on the genic modifiers of yellow present (C series, F, f) regardless of whether the hair was black or yellow, except that it was greater in blacks than in the corresponding yellows. It is concluded that the technique used yields only an enzyme specific for yellow pigmentation.

Extrachromosomal heredity.—The question of possible autonomy of cytoplasmic components is important. The usual criterion is a difference in reciprocal crosses, maintained for at least two generations. Harvey (115) describes the plutei from four echinoderm crosses as almost wholly maternal. But as only the first generation could be produced, it is impossible to decide between cytoplasmic heredity, maternal influence, and determination by products of the egg nucleus before fertilization. Moreover in one of the cases (*Strongylocentrotus purpuratus* ♀ × *S. franciscenus* ♂) a statistical study of the more important form indices by Moore (116) indicates that the hybrid actually is almost exactly intermediate, although necessarily like the maternal species in absolute size.

Russell & Green (117) note briefly a marked matroclinous difference between reciprocal hybrids of two inbred strains of mice which differ in number of lumbar vertebrae (usually five and six respectively). The difference did not persist in large F_2 generations and thus was presumably due to maternal influence.

Gowen (118) has studied the influence of the various chromosomes and possible extrachromosomal materials on the heterosis found in crosses between inbred strains of *Drosophila melanogaster* of different geographic origin. No extrachromosomal effect was indicated.

An immediate effect of recessive mutations on the microspores (haploid) of diploid *Tradescantia* has been found by Rick (119) by x-radiation shortly after meiosis. There was increased variability, decreased size, and increased percentage of abortion. Similar treatment of autotetraploid species showed no significant effects.

Drosophila virilis and *D. americana* differ markedly in many respects. Stern, Schaeffer & Spencer (120) have shown by carefully controlled back-crossing for many generations that no appreciable portion of this difference is transmitted along the straight female line.

There are, however, other cases in which extrachromosomal heredity is indicated. Michaelis (121) describes experiments designed to carry further the analysis of deleterious interaction effects of persistent cytoplasmic components of *Epilobium hirsutum* with genes from other strains of *E. hirsutum* or another species, *E. luteum*. Villerts (122) describes differences in reciprocal crosses in the genus *Begonia*.

Most known cases of apparent extranuclear transmission are concerned with chlorophyll deficiencies in certain species of plants. An important new result in this field is one obtained by Rhoades (123) in connection with white striping of corn due to the recessive gene ij (iojap). The cross IjIj ♀ × ijij ♂ produces only green offspring in F_1. The reciprocal cross produces white and striped seedlings as well as green ones. Sometimes all seedlings from an F_1 ear are white. The cross, striped Ijij × unrelated IjIj, sometimes produces only green plants, in other cases green striped and white, and occasionally 100 per cent white although in the last case half of the seedlings should be IjIj. It appears that in genotype ijij there is a tendency toward mutation in the plastids and that mutants continue to multiply as of the deficient sort and to be

transmitted as deficient plastids along the straight maternal line in spite of restoration of the nucleus to homozygous normal.

There is at least a certain formal similarity between this observation and a series of remarkable results obtained by Sonneborn (124) with *Paramecium aurelia*. The most thoroughly analyzed case concerns a strain in which the individuals secrete a substance that kills individuals of other strains in the course of forty-eight hours. Conjugation can be obtained between the two strains. The descendants of the killer exconjugant remain killers as long as there is no nuclear reorganization. Those of the sensitive exconjugant remain sensitive. Since conjugation results in identical micronuclei and degeneration of macronuclei with reformation from the micronuclei, these results seem to indicate extranuclear heredity. Autogamy, however, results in segregation of killer and sensitive clones from the killer F_1 (Kk) indicating a pair of nuclear alleles. Moreover backcross tests reveal that the sensitive F_1's also carry the killer gene in heterozygous condition (Kk). It appears that there is an extranuclear substance (kappa) which persists and multiplies in the presence of gene K, is lost after a few fissions in the absence of K, but cannot be produced, if absent, by action of K. Crosses between the killer line KK (kappa) and a sensitive line KK (no kappa) simulated pure cytoplasmic heredity. Later experiments (125) have brought out certain complications which seem to indicate that kappa is taken up by the macronucleus and multiplies therein. Less exhaustive studies indicate that this mode of inheritance applies to all of eight other pairs of characters studied in the same variety. In other varieties of *Paramecium aurelia*, there is no indication of such semiautonomous extranuclear components.

Genes in relation to growth and differentiation.—Genetics is concerned with growth in two very different ways. Growth is naturally modified by a great variety of physiological conditions. It is not surprising that crosses of large and small varieties should usually reveal multiple factors. Powers (126) has studied the inheritance of a 56-fold difference in size of fruit in tomatoes. Results in F_1, F_2, and backcrosses conform fairly well to expectation under multiple factors with multiplicative effects but not at all under the hypothesis of additive effects. Smith (127) in a study of corolla length in derivatives of small flowered *Nicotiana Langsdorfii* and large flowered *N. Sanderae* compares various triploid and tetraploid types. He finds that chromosome replacements have more nearly

multiplicative than additive effects. Castle (128) presents data on certain genes of the mouse, recognized by effects on color, but with incidental effects on size. MacArthur (129) describes the effects of selection of strains of mice for large and small size which incidentally brought about differentiation in other characters (color, activity, relative lengths of ears, feet, and tail, and fecundity) presumably in the main because of multiple effects of the genes.

Growth, however, is in itself a process closely allied to heredity. Both consist of the multiplication of highly specific molecules. Step by step synthesis of the growth proteins, analogous, at a higher level, to the step by step synthesis of arginine in *Neurospora* discussed above presents difficulty (cf. Stern, 130). Autonomous duplication of the proteins in the cytoplasm is an alternative that also presents difficulties. If continuing along the germ line, it should result in cytoplasmic transmission of protein specificity, but as indicated by references cited here and by much earlier work, all studies of the genetics of specificity have indicated genic control. Another alternative is synthesis exclusively by nuclear genes (perhaps in the heterochromatin). Finally there is the possibility of cytoplasmic multiplication in the somatic cells subject to decay and ultimate nuclear control. The apparent active transfer of nucleic acid from nucleus to cytoplasm in cells that are rapidly dividing or about to do so may be pertinent (131). So also may be the nucleoprotein content of microsomes and mitochondria which Claude (132) suggests may be self-duplicating cytoplasmic bodies.

A related problem is the nature of the more or less permanent differentiation of cells in development, which from the standpoint of the cell as an organism constitute changes in cell heredity. The question whether such changes are nuclear (induced gene mutations in at least a formal sense) or are cytoplasmic, either as permanent changes in autonomous cytoplasmic components, or in the cytoplasm as a single self regulatory system, is of fundamental importance in physiological genetics but is a matter on which there is little evidence. The site of enzyme synthesis is, however, pertinent. The fact that isolated microsomes and mitochondria have various enzymatic properties (133) is at least compatible with the hypothesis that differentiation is cytoplasmic. Other observations, however, point to the nucleus as the site of enzyme synthesis in differentiated cells. Thus Krugelis (134) notes great alkaline

phosphatase activity in the salivary chromosomes of *Drosophila*. Isbell *et al.* (135) note the presence of appreciable amounts of B vitamins in isolated nuclei of beef heart and of mouse cancer, which finding suggests the presence of enzymes of which those vitamins are the prosthetic groups. Biesele (136) finds that chromosome size in normal rat organs varies in close parallelism with the total concentration of B vitamins (excluding inositol) while there is no such parallelism with total nuclear size, amount of cytoplasm, or development of plasmasomes. This does not apply to cancer cells (137) in which nuclei appear to be large because of multiplication of strands (indicated by considerable overt polyploidy but especially by multiplication of sets of plasmasomes) rather than because of the functional hypertrophy of large chromosomes in normal cells.

There are many genes whose effects seem to be restricted to particular kinds of cells—epidermis, nerve, sense cell, pigment cell, cartilage, etc.—but most of them are probably genes that find their substrate for action only in a particular class of differentiated cells rather than ones concerned with the differentiation process itself. Studies of pigment cells have already been considered. Other cases of tissue limited gene action will be considered in the next section. We may note here the detailed studies of gene controlled anemias in mice by Grüneberg. In one (138), recessives exhibit a flexed tail and often a white belly spot in addition to anemia at birth. The first generation of red blood cells, large, nucleate, produced in the yolk sacs are normal. These are replaced by smaller enucleate cells from the liver and later the bone marrow, which tend to be siderocytes, characterized by easily detached iron. The still smaller definitive red blood cells, which appear shortly after birth in normal mice are much delayed in appearance in the anemics and never fully replace the siderocytes in them. Another type of anemia associated with semidominant black eyed white has a wholy different basis. The anemia is of the macrocytic type as in human pernicious anemia. There are two mutant alleles with pleotropic effect of a puzzling sort (139).

Genes and morphogenesis.—All of the many papers on the genetics of morphological characters have physiological implications. A list of lethal and sublethal characters in farm animals (140) is instructive with respect to the nature of the more serious mutations.

In general, one notes a marked contrast between the simple direct relation of gene to character usually observed in the cases of antigenic specificity, or of single metabolic steps, and the complex and highly variable relations usually found between genes and morphological characters.

An autosomal recessive, determining the character "naked" in pigeons (141), may serve as an example of a gene which affects one tissue in a rather extreme but uniform way. More typical is the case of the character "ragged" in the fowl (142) also an autosomal recessive but expressed in only about 50 per cent of the cases and when expressed, varying from a slight reduction to complete elimination of primaries and secondaries. Microphthalmia in the mouse is another example of variable penetrance and expression. In this case, two major genes were indicated (143).

These are abnormalities of defect but the same principles apply to abnormalities of excess. Polydactyly of the fowl depends on an irregular semidominant (144). Variation in penetrance could be controlled to some extent. A moderate reduction in temperature during a critical period in incubation tends to suppress the character (145). Slifer (146) describes a mutation of *Drosophila melanogaster* which tends to bring out sex combs on the second and third legs of males as well as lengthening those which normally appear on the first legs. Here again there were thresholds and environmental effects (penetrance increasing from 9 to 93 per cent with increase in yeast in the medium). A well defined anterior-posterior gradient in occurrence and extent was brought out. Villee (147, 148, 149) has made detailed studies of the effects of temperature and genic modifiers on the effects of several other homoeotic genes of *Drosophila melanogaster*. Thus treatment of low grade aristopedia (ss^{a-B}) with cold (14°) during a certain period tends to increase the number of leglike segments of the arista, beginning at the base. Heat (29° to 35°) has the reverse effect on this series of alleles. The effects on proboscipedia are just the opposite, aristalike oral lobes after cold treatment, leglike ones after heat. An arista modifier (al) affects arista-like parts only. A number of genes with major effect on the legs (d, ds, fj, cg) modified the character of aristapedia while the latter in turn modified the effects of these genes on the legs. The effects of d, ds, fj, and cg had previously been studied embryologically by Waddington (150) who found unexpected and sometimes homoeotic effects of these genes

in combination. Glass (151) produced somewhat palp-like protrusions from the eye of *Drosophila* by x-ray treatment of embryos of a certain stock with morphologically normal eyes but shown to carry a favoring gene while other stocks lacked this and might carry a suppressing gene. Sawin (152) finds multiple factors to be responsible for homoeotic variation in the number of ribs and of presacral vertebrae of rabbits. The development of a prostate gland in female rats by inbreeding and selection, the reaction of which to hormone treatment has been discussed by Mahoney (153), is at least related to this class of variations. It is clear that these genes do not stand for the structures that replace normal ones, in the sense of complete determiners. They act rather as switches which call forth a more or less normal developmental reaction in a portion of the body in which this reaction is normally below the threshold.

While gene action seems highly localized in some cases, widespread effects are more common. A mutation of the mouse characterized by screw tail shows abnormalities also in sternum, pelvis, vertebral column, skull, and teeth (154). Another mutation of the mouse (155) has small ears and imperfect xiphisternum as well as small general size. Grüneberg (156) in connection with congenital hydrocephalus of the mouse, a case in which multiple effects appear to trace to one tissue, the cartilage, makes a distinction between spurious pleiotropism, of which this is an example, and possible genuine pleiotropism in which distinct primary actions of the same gene are involved. Another gene which he describes (157) —fidget—which combines abnormal behavior (head shaking, circling) with ultimate deafness, lesions of the cornea, and polydactylism, might seem an example of genuine pleiotropism but he holds that as a working principle it is desirable to assume that all cases are really spurious.

A renewed attack on the question of the prevalence of multiple effects of genes has been made by Dobzhansky & Holz (158). Visible mutations were induced in an isogenic stock by means of x-rays and studied for differences from type in respect to a seemingly unrelated character, the form of spermatheca. In most cases (14 out of 19) there were significant differences, though smaller ones than in an earlier study in which it was attempted to make a mutant isogenic by repeated backcrossing to type. They were greater, however, than observed by Schwab in an experiment similar to

the latter. The fact that all of the significant deviations from type were in the same direction suggests some general effect such as that of many mutations on viability and fertility.

Baumann & Landauer (159) find a correlation between occurrence of extra toes (usually asymmetrical) in polydactylous fowls and just those motor cells in the spinal cord concerned with innervation of the leg and foot. In view of experimental evidence, it is clear that the peripheral effect is primary.

Histological studies of the effects of genes such as Bar and eyeless of *Drosophila* on facet number and optic ganglia led to the conclusion that the effects on the latter are wholly dependent on the former by way of contributions from centripetal nerve fibers from the visual cells (160). Steinberg (161, 162) has carried the analysis of various eye mutants (Bar, Lobe alleles, eyeless) a step back to reductions in the number of cells entering into the eye discs, cells capable of forming either head chitin or facets depending on extrinsic and intrinsic factors. Waddington & Pilkington (163) have studied certain other genes of *Drosophila* with morphologically more abnormal effects on the eye, facet alleles, lozenge alleles, morula, and ophthalmapedia, the last of which carries us back to the homoeotic group. Abnormal histogenesis is attributed to abnormal folding rather than the reverse.

One of the most thoroughly studied cases of pleiotropism is that of the homozygous Creeper fowl. While the effect seems localized in the legs in heterozygotes, in homozygotes most of which die between 55 and 80 hours (prothanics) and all before hatching, the abnormalities are so general as to suggest some general metabolic disturbance. Most of the pathological symptoms of the prothanics, however, can be traced experimentally to one source (164), defect of the yolk sac circulation which is recognizable at 54 hours (23 to 27 somites). Defects of the eye (coloboma, virtual absence of sclera) which appear later may also depend on defective blood supply. Both normal and CpCp vesicles, transplanted to the orbit of a normal, developed normally (165). Both developed coloboma in an abnormal site (flank) of a normal embryo. A normal eye in the orbit of a homozygous Creeper showed all the defects of an eye of the latter. On the other hand, transplants from the leg and wing forming regions of five to eighteen somite embryos from Cpcp×Cpcp transplanted to noncreeper host, showed typical

phocomelia in 25 per cent (CpCp) in contrast with 75 per cent normal (Cpcp and cpcp). Apparently this aspect of the syndrome is localized too early to be due to circulatory defects (166).

Extreme apparent localization of effect in heterozygotes is associated with widespread effects in nonviable homozygotes in several tail abnormalities of the mouse. Dunn & Gluecksohn-Schoenheimer (167) found that a certain syndrome, simultaneous failure of post gut and urinary duct, sometimes including absence of kidneys, ureters, genital ducts, and bladder, may occur in a considerable number of genotypes with otherwise diverse effects.

Gene action in the earliest stages of development are of great interest. Poulson (168) finds that chromosome deficiencies involving the notch locus of *Drosophila melanogaster* bring about a characteristic distortion of the normal developmental pattern in which the entire nervous system shows hypertrophy associated with delay in differentiation. Robertson (169) has made a new study of the homozygous yellow mouse which he finds to develop normally through cleavage and blastocyst but to die after the trophectoderm has come in contact with the uterine epithelium. There is slightly more development in the uterus of a nonyellow female.

Dunn & Gluecksohn-Schoenheimer (6, 170) have continued their studies of the effects of the various alleles of brachyury in mice. T/+ has a short tail, while T/T, which dies at ten and three-fourths days, lacks notochord and posterior portion of the body, $t^0/+$ and $t^1/+$ are normal, t^0/t^0 dies at about five days with no mesoderm or notochord, and t^1/t^1 dies still earlier before development of the embryo proper begins. The heterozygous combinations of these lethal genes can be produced by suitable matings. Combinations T/t^0 and T/t^1 are viable tailless mice while t^0/t^1 may be either viable with a normal tail or die early, with microcephaly but normal tail. The partially complementary action of these lethal alleles has already been referred to. The observation that genes, whose effect seems in general to be most severe on the posterior part of the body, should in one combination tend to produce a normal tailed microcephalic brings out again the point that the localization of gene effects is to be sought more in the properties of the organism than in the gene. The situation calls to mind that found in the experimental production of monsters by early treatment with deleterious agents. The dominant region in the physio-

logical gradient is that most capable of acclimatization to long continued treatment with low concentrations but is also the most sensitive to brief treatment with lethal doses. The microcephaly of t^0/t^1 under this view would indicate a short period of complete lack of complementarity of t^0 and t^1 while the predominantly posterior inhibition of T/T, the taillessness of T/t^0 and T/t^1, and short tail of T/+ would indicate longer periods of less extreme metabolic defect.

The morphologic effects considered so far indicate that the array of genes determine a system with a high capacity for self regulation. Disturbances of metabolism, genic or environmental, often localized specifically in one tissue or another, are further localized in immediate effect by a threshold in a gradient of adaptive capacity. More widespread effects are determined by correlative influences. In another class of genetic changes, the disturbance of regulatory capacity takes the form of uncontrolled multiplication of particular cells. Russell (171) describes the genetics of a tumor of *Drosophila melanogaster* which depends on one principal gene but also on genic modifiers, with nongenic factors responsible for a threshold. Gordon (172) is continuing his studies of melanomas of fish hybrids in which specific pigment genes with no abnormal effects within a pure species produce uncontrolled melanomas in the hybrids.

In a wholly different category is the observation of Wooley, Law & Little (173) of the restoration of high incidence of mammary carcinoma by injecting whole blood from a high tumor strain into mice tracing to this strain but exhibiting low tumor incidence for two generations following foster nursing on a low tumor strain. The "gene" in this case is neither in the chromosomes nor the cytoplasm of the germ cells.

Genes and behavior.—Many genes with effects on morphology necessarily affect behavior because of the nature of the morphological defects. A systematic study of the effects of mutations of *Drosophila melanogaster* on power of flight has been made by Williams & Reed (174), using a stroboscopic method. In some cases the reason for an observed effect was obvious but in others was quite obscure The optomotor responses of various *Drosophila* mutants (175) could usually be correlated with morphology or color of the eye but not always. Scott (176) describes certain differ-

ences in behavior of *Drosophila* mutants, the reasons for which are not obvious. Keeler & King (177) find characteristic differences in temperament and behavior of color mutants that arose within a colony of Norway rats and so may be presumed to be pleiotropic effects of these genes.

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DEPARTMENT OF ZOOLOGY
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DEVELOPMENTAL PHYSIOLOGY

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One who attempts to review the acquisitions of a year or two in any branch of science is likely to find himself in the position of a man with a house already well stocked with furniture who receives an assortment from a variety of donors. His task is to fit the individual pieces together with his own into a harmonious setting. For some pieces he is likely to find no suitable place and so be obliged merely to catalogue them and store them until a time comes when they will fit into some larger scheme. Such at least I have found to be my own position. To limit the task I have confined my efforts to organizing the results of investigations dealing primarily with metabolism, the vascular system, and the nervous system: the three aspects of developmental physiology which have been most actively investigated during the past year. Other aspects of the subject—the structure of the amphibian egg (1), the developmental physiology of the sea urchin (2), development and the evolution problem (3), the development of form (4), and of vertebrate pigment cells—have been reviewed elsewhere (5).

Mechanics of Development

The studies of Holtfreter (6, 7) on the mechanism of gastrulation in *Amblystoma punctatum* should be read by every investigator, teacher, and student of embryology, for they form the outstanding contribution to our knowledge of this process since the rich contributions of vital staining techniques in the Twenties. Holtfreter traces the movements of the several regions of the embryo in gastrulation to basic properties in cell groups as expressed by their structure and by specific responses to their environment. The integrated character of the movements of cells during gastrulation is shown to be the result of the peculiar arrangement of these cell groups which differ in internal composition and kinetic behavior. This peculiar predisposed arrangement of groups of cell so different from one another appears to be a consequence of the organization of the unfertilized egg and the process of segregation. The way is now open for metabolic studies on the cell types on which Holtfreter has so sharply focused attention.

Metabolism in Development

Histochemistry.—Our knowledge of metabolism in development continues to be broadened by histochemical studies in which restricted staining reactions and ultraviolet light are used to locate specific substances within the embryo and fetus. Of special importance are the studies on the distribution of pentose nucleic acids—the subject of an excellent review by Brachet (8). Evidence is fast accumulating which indicates that desoxyribonucleic acids are restricted to the nucleus and ribonucleic acids to the cytoplasm of animal cells (9). Complexes of phospholipid with nucleoprotein containing ribonucleic acid are formed in embryonic tissues (10) as well as in the active fraction of tumor sarcoma extracts (11). The biological activity of ribonucleic acids has been further emphasized by the demonstration of their presence in the tissue growth promoting factor of embryonic juice (12) as well as by the presence of high concentrations of ribonucleotides in the cytoplasm of cells in which rapid protein synthesis is known to be occurring (13 to 17). When adult and embryonic tissues of the sheep are compared, the total nucleic acid content as measured by nucleoprotein-phosphorous estimations, is found to be higher in the latter than in the former. However, the ratio of ribonucleic acid phosphorus to desoxyribonucleic acid phosphorous is either of the same order in the embryo and adult tissues or slightly higher in the latter (18). The growth stimulating substance "Embryonin" of Fischer (19) may prove to contain ribonucleic acid for it is not macromolecular and it is a nucleoprotein.

Using the nitroprusside method to reveal the presence of proteins containing sulfhydryl groups Brachet (20) has followed their location and concentration in developing fish, chicks, and amphibia, giving particular attention to the latter. During organogenesis the concentration of protein with sulfhydryl groups is greatest in the most active centers of growth and differentiation as indicated by the developmental sequence: neural plate, tail-bud, notochord, somites, sensory placodes, optic vesicles, and enteron. The distribution of acid-soluble phosphorus and of ascorbic acid have also been followed in the developing hen's egg (21) and in the chick respectively (22, 23).

Enzymes.—The distribution of enzymes of specific types within embryos continues to be investigated as the first step toward the discovery of the biochemical reactions which underlie tissue differ-

entiation. In chick embryos cytochrome oxidase (24) has been demonstrated to be present as early as the head process stage. The total enzyme increases up to the middle of the second day and maintains that level through the fourth.

Both alkaline and acid phosphatases are present in the unincubated blastoderm of the hen's egg (25, 26, 27) and in all the embryonic tissues developed from it during the first two or three days of development. The concentration of the alkaline phosphatase is much greater than that of the acid. The phosphatases appear to play an important role in the early differentiation of the conducting elements of the nervous system (28). In extracts of chick embryos the oxidation-reduction reaction between pyruvic acid and triosephosphate from hexosediphosphate occurs rapidly in the presence of phosphate acceptors (29). The addition of a coenzyme system increases the speed of the reaction to the order of that of glycolysis in living tissues. Chick embryos four to nine days old contain 1.5 to 3 mg. of coenzyme per gram of dry weight. Crude whole chick embryo extracts contain an aminopeptidase (30). The accumulation of this enzyme like that of dipeptidase and other entities in the developing chick shows abrupt changes in rate (31, 32).

The chemical development of the liver of the rat has been studied with particular attention to the relative masses of the extra and intracellular phases (33); nucleo-cytoplasmic ratios were estimated. Peptidase increases before birth; glycogen accumulates as birth approaches and drops afterward, as it does in the guinea pig and in other forms. The nucleo-cytoplasmic ratio and the phosphorus content of the liver cells decrease together as development advances. There is no carbonic anhydrase in the embryonic tissues of the rat (34).

Energy releasing mechanisms.—As a result of the studies of Parnas & Krasinska (35) on respiration three critical periods are recognized in the metabolism of the developing amphibian embryo, i.e., gastrulation (see also 36), the formation of medullary plate and neural groove, and the appearance of the gills. These critical periods are marked by discontinuities in the rate of oxygen consumption. For example, the normal oxygen consumption in *Rana pipens* increases exponentially with age from fertilization until the 3 mm. stage; there is a marked discontinuity at the time of gastrulation and a second at the time of formation of the neural

folds (37). Development from the first cleavage to blastula formation proceeds in the absence of oxidative systems but not without the energy transforming systems which are inhibited by urethane, i.e., the dehydrogenases. The onset of gastrulation and of neural fold formation are inhibited by azide and by cyanide; the former attacks the Warburg-Keilin energy transforming system presumably at the cytochrome oxidase level; the latter acts as a respiratory inhibitor by uniting with the metal groups in respiratory catalysts such as cytochrome oxidase. Monoiodoacetic acid, which inhibits glycogen breakdown by inhibiting oxidation of triosephosphate (38), does not appear to inhibit development up until the neural plate formation, whereas it completely inhibits the formation of the neural folds. This observation is in keeping with the report of Brachet (39) that inhibition of aerobic glycolysis did not kill the embryo until it reached the stage of neural fold formation.

In short, evidence continues to accumulate which indicates that each of the so called critical periods in the development of the frog, gastrulation, neural plate formation, etc., is associated with the development of new sources of energy.

Of especial interest and importance in this field of metabolism is the study of Orstrom (40) on the nitrogen metabolism of the sea urchin egg during the period immediately after fertilization or after stimulation by appropriate concentrations of sodium chloride; published in 1941 Orstrom's study has only recently appeared in this country. Fertilization and stimulation by salt solutions are followed by a break down of glycogen, the release of ammonia and some amino compounds which stimulate respiration. The ammonia content of the eggs increases 30 to 40 per cent within ten minutes but returns to its former level in three hours. An unknown substance, probably glutamyl peptide, is formed at the same time as the ammonia. The deaminase of the pulp of the eggs hydrolyzes adenylic acid to adenosine, which loses ammonia to become inosine. The hydroxypurine content of the eggs rises after fertilization, a fact which lends support to the possibility that the same sequence occurs in the egg. The author's views of the significance of these reactions are presented at some length and should be read by all those who are working in this very specialized field of embryology.

Determinations of the oxygen consumption, which represent the first stage in analysis of the metabolism and energy releasing mechanisms are difficult to make on mammalian embryos and

fetuses. Recently, however, Kleiber *et al.* (41), using the Warburg microrespiration apparatus, estimated that thirteen day old rat fetuses weighing 77.3 mg. consumed 55 ± 3 c. mm. of oxygen or about 0.12 cc. per gm. per min. This is of the same order as the rate of oxygen consumption of the adult rat and almost identical with the figure given by Lussana (42) for the chick between the fourteenth day of incubation and hatching. It is quite in contrast, however, to the figures given by Barcroft and his collaborators for the goat fetus (43), ($.0026 \pm .0006$ cc. per gm. per min.), and for sheep fetuses (44), (.0048 cc. per gm. per min.—average of seven estimations). The difference is possibly due to differences in the degrees of development and it serves to emphasize the limited value of isolated estimations and the great need for such determinations at all stages of gestation.

The influence of external agents.—The influence of ultraviolet irradiation (2800 Å twenty minutes) on the development of *Rana pipens* and *Rana fusca* (45, 46) has been assessed by comparing the ratio of the volume of the notochord to the volume of the somites on the two sides with that in normal controls. This ratio, assumed to be an index of a morphogenetic potential, is generally increased by irradiation of the unsegmented fertilized egg, the two-, and the four-cell stages; it tends to be reduced after irradiation of the blastula and gastrula. Intermediate stages give intermediate ratios. Morphological expressions of the effect of external agents on development give little evidence of the energy releasing mechanisms which are stimulated or whose action may be impaired by the agent (47 to 55). It is to be hoped that the parallel growth of our knowledge of the action of ultraviolet light upon proteins and enzyme systems will permit an expression of their effects on development in biochemical rather than morphological terms.

The Vascular System and the Placenta

Fetal blood.—Electrophoretic comparisons of the protein components of human adult and fetal plasma taken from the placenta vessels reveal that there is very little difference between the two (56, 57), nor do osmotic pressure measurements point to any marked difference between the properties of fetal and adult horse serum albumin (58). If the conditions are the same in the fetal and maternal sheep serum the high osmotic pressure per unit of

protein (59) in the former must be attributed to the globulin fraction. See also (60).

The peculiarities of the composition and properties of fetal erythrocytes, as compared with maternal, continue to hold interest. McCarthy (61) has confirmed and extended the older observations of Haurowitz (62) and Hill & Wolvekamp (63) which indicated that the hemoglobin of the human fetus has a greater affinity for oxygen than has that of the maternal organism. This relationship is reversed in suspensions of corpuscles, for the maternal corpuscle causes a marked decrease in the oxygen affinity of the hemoglobin in it whereas that of the fetal corpuscle is not appreciably altered by encapsulation. These observations will stimulate research upon the nature of the "ghost" of the fetal corpuscle and upon the arrangement of the hemoglobin within it.

The fetal circulation.—Recent studies on the fetal circulation (64, 65, 66) have reestablished the view expressed by Wolff a century and a half ago, that the termination of the posterior (inferior) caval channel is bifurcate; one fork leads in to the left, the other into the right atrium; the excellent study of Keen (67) on human fetal hearts describes the changes which this bifurcation undergoes as development advances. The left fork diminishes in size whereas the right enlarges. Hand in hand with this shift there appears to be an increase in the proportion of the return from the inferior cava which is directed into the right side of the heart. The course of the two caval streams through the heart appears to depend upon the stage of development, a view which is in harmony with the studies on the blood gases. These and other aspects of the fetal circulation have been the subject of a review (68).

The mechanisms responsible for the timing of the closure of the ductus venosus, the ductus arteriosus, and the foramen ovale at birth remain undiscovered. Some doubt has been cast upon the suggestion of Kennedy & Clark (69) that the ductus closes when the blood perfusing it is nearly saturated with oxygen, by experiments (68) in which saturated blood was allowed to enter the right side of the heart before breathing of the fetus began. The ductus failed to close under these circumstances. The patency of the ductus appears to be intimately related to the circulation through the lungs (70), a fact which suggests that the ductus closes when the pressure on the right side of the heart is permitted to fall by the decreased resistance in the lesser circulation which results from

the inflation of the lung. Keen (67) has shown in the human fetal heart, as had long been suspected, that when the fluid enters the left atrium via the pulmonary veins at a pressure greater than that at which fluid is perfusing the inferior caval channel none from the latter enters the left atrium, for the foramen ovale is blocked by its valve. A reduction in the "pulmonary venous" pressure below that of the pressure in the inferior cava permits the foramen ovale to open. Unfortunately pressures are not given.

Evidence has appeared for the first time which indicates that the ductus venosus in the sheep (71) is more than an inert structure and that it has a physiology. At its proximal end the ductus venosus is enveloped by a band of muscle arranged in the form of a sphincter (72). This muscle is supplied with motor type endings by nerve fibers which leave the two vagi and form a common trunk enroute to the ductus. Unlike the portal vein there are no nerve cells in the walls of the ductus, a fact which suggests that the motor fibers ending in its musculature are sympathetic rather than parasympathetic. This sphincter appears to regulate the proportion of the blood returning from the placenta which flows through the liver capillaries enroute to the heart, for Barclay *et al.* (71) have observed that the flow through the ductus may cease abruptly only to begin again a few seconds later. The circumstances under which the sphincter contracts *in utero* are unknown, but it appears to be the mechanism responsible for the closure of the ductus at birth and may well be under control of the vasopressor center.

The nerve fibers which supply the ductus venosus do not extend beyond it to the proximal portion of the umbilical vein. However, nerve fibers are present on the abdominal portions of the umbilical arteries of both man and the guinea pig, though the extra-abdominal portions are devoid of nerves (73). The origins of the fibers which supply the abdominal portions of the umbilical vessels and their possible functional role remain to be discovered.

The placenta.—The oxygen consumption of the human placenta, as determined in the Warburg apparatus (74), decreases from 5.3 cc. per mg. of dried tissue per hour early in gestation to about 1.7 cc. near the end of term. These values are surprisingly high when compared with the figures produced by other studies on the human (75, 76, 77) and the rat (78) placenta, though the circumstances under which they were obtained appear to be open to less

criticism. With an oxygen consumption of the order of .08 cc. per min. per gm. of tissue it is impossible to regard the placenta as an inert membrane between the fetal and placental circulations. Its metabolic rate during the early part of gestation puts it in the class with the more active glands and in this connection it is of interest that the gradual decrease in oxygen consumption with advancing gestation is correlated with changes in the chorionic epithelium, in particular with changes in the layer of Langhans and with syncytial degeneration at the end of term. The cells of Langhans appear to be responsible for the production of cyonin, the chorionic gonadotropin, a circumstance which suggests that the high oxygen consumption may be associated with the synthesis (79). The chorionic epithelium of which Langhans' layer is the inner cytotrophoblast was shown some years ago to be the layer which prevented the diffusion of ferric ammonium citrate (80) and trypan blue (81) from the maternal to the fetal circulation in pregnant cats, though in rabbits the citrate crossed the fetal epithelium. The recent studies by Flexner and his colleagues (82, 83) on the rate at which radioactive sodium, Na^{24}, was transferred across the different morphological types of placentae also point to the importance of the chorionic epithelium in limiting exchanges between the maternal and fetal blood streams. Specifically, Gellhorn *et al.* (84) found that in the human after nineteen weeks of gestation, when Langhans' layer has almost completely disappeared, the rate at which sodium crossed the placenta per gram of tissue increased markedly. A similar increase in transfer rate occurs in the rabbit placenta when the syncytium becomes discontinuous about the twenty-fifth day of gestation.

A comparison of the transfer rate across placentae of each of Grosser's four classes (82, 83) shows quite clearly that the greater the number of layers in the barrier between the two blood streams the slower the rate of transfer with the same concentration of radioactive sodium in each case in the maternal blood. There is, however, one very surprising feature in the comparison; the transfer rate across the hemochorial (rabbit) placenta is about ten times greater under similar conditions than it is across the endothelial type (cat). The only tissue element present in the latter which is absent in the former is the endothelium of the maternal capillary. It is difficult to believe that the absence of such a readily permeable layer as the capillary epithelium is responsible for the tremen-

dous difference; it seems more probable that the differences in permeability are linked with differences in the relative surface area of the two types.

The decline in the transfer rate of sodium across the placentae of the forms (the sow excepted) which Flexner and his colleagues studied appears to be paralleled by a decrease in the rate of oxygen transfer, for the percentage saturation of the blood in the umbilical vein of the fetal lamb tends to fall sharply near the end of term (68). The decrease in permeability of the placenta rather than the continued growth of the fetus may be the underlying cause for the decline in the oxygen saturation of the blood from the brains of rabbits retained *in utero* by maternal injections of progesterone and pregnancy urine (84). The oxygen capacity rises until the thirty-fourth day. Under these circumstances the rabbit fetuses pass through a period of moderate to one of profound anoxemia and ultimate death.

These observations cast considerable doubt upon the contention of Synder & Rosenfeld (85) that the respiratory movements of postmature fetuses *in utero* are not caused by oxygen lack.

Other factors which must influence the rate of transfer across the placental barrier are the surface areas of the capillaries, their arrangement, and the relative directions of blood flow in maternal and fetal vessels. In the cotyledonary placenta of the sheep the fetal and maternal capillaries have been found (86) to be arranged as they are in the rabbit, guinea pig, cat, and ground squirrel, i.e., so that the blood streams in them pass in opposite directions; this arrangement permits the fetal blood leaving the placenta to be in equilibrium with the entering maternal blood. The length of the parallel sets of capillaries and their proximity increase as gestation advances. These observations make possible the calculation of the diffusion coefficient of the placenta of the sheep, i.e., the number of cubic centimeters of oxygen transferred per minute for each mm. Hg. of gas pressure difference on the two sides. The calculation uses some of the data of Barcroft *et al.* (87) on the oxygen consumption of the fetus and the minimal blood flow through the fetal and maternal sides of the placenta. The data in two cases yield diffusion coefficients of 0.1 and 0.3 for placentae in the last third of gestation. The coefficient often given for the lungs of man is forty.

A most challenging addition to our knowledge of the exchanges

which occur between the maternal and fetal blood streams in the placenta has resulted from the recognition (88) of the relationship between erythroblastosis fetalis and the blood factor identical or related to the Rh (Rhesus) agglutinin first described by Landsteiner & Wiener (89). The steps involved appear to be iso-immunization of the mother by blood factors inherited and dominant in the fetal blood, then the subsequent passage of the agglutinin formed in the maternal blood through the placenta and finally their continuous action upon the susceptible fetal blood with hemolysis of the red cells. The Rh factor is inherited as a simple dominant mendelian character. Rh-individuals appear to form about 15 per cent of the population; an Rh-mother inseminated by an Rh+ father bears a heterozygous child Rh+. The maternal blood may produce anti-Rh agglutinin as a result of immunization with Rh+ fetal blood. Since the Rh factor appears to be limited to the red corpuscle the possibility must be recognized that fetal red cells in one form or another leave the fetal circulation, penetrate the chorionic vili to enter the maternal blood stream, and unless it is shown that such a transference is unique to the placenta of the Rh− mother we must assume that it is a normal occurrence during gestation. The transference of the antibodies of the tubercle bacillus across the human placenta has been investigated (90).

The role of the placenta as a transitory liver has been emphasized by the demonstration of carbohydrate and fat storage in the guinea pig placenta (91). Fat is stored in both the fetal and maternal portions though the concentration is always greater in the fetal. This is likewise true when fat concentrations in the fetal and maternal livers are compared. Glycogen is stored only in the maternal portion of the placenta; it appears first in the fetal liver about the 55th day. The fetal blood glucose level is generally lower than the maternal although occasionally the condition is reversed. Vitamin A levels in human maternal and fetal blood also vary considerably. There appears to be no constant relationship between them; raising the maternal level does not alter the fetal level beyond normal values.

The establishment of reserves of glycogen and fat in the fetal membranes and in the maternal portion of the placenta may be linked with the rich blood supply to the uterus early in pregnancy

before the fetus has attained any appreciable size, for the supply is in excess in relation to the fetal oxygen requirements (92).

The Nervous System

Investigations on the developing nervous system tend to fall into one of two categories, i.e., studies primarily concerned with morphogenesis or those which describe its functional development.

Morphogenesis.—The older views that the folding of the neural plate is due either to cell proliferation, cell enlargement, or a combination of the two derive no support from recent investigations (93, 94, 95), nor is differential swelling of the neural plate due to hydration to be regarded as the cause of the folding. The current morphological studies indicate that the folding may be a direct result of a one sided contraction process involving the exposed surface of the neural plate cells. The folding process is inhibited in chick embryos irradiated between the primitive streak to the eight-somite stage with monochromatic ultraviolet light (96), whereas cell division and volume changes are not obviously affected. The effect on the folding is thought to be wrought through the action of the ultraviolet light upon sterols which may very well take part in the formation of the internal limiting membrane of the plate.

The "surface coat" of Holtfreter (97) may play an important role in the formation of neural tubes by gastrula ectoderm of *Amblystoma punctatum* in the absence of the organizer, a capacity of the ectoderm first demonstrated by Barth (98) and recently confirmed by Holtfreter (99), though the latter investigator was unable to obtain neural tubes from gastrula ectoderm of *Triturus*. Holtfreter's suggestion that the gastrula ectoderm is, under the conditions of Barth's experiments, induced to form neural tubes by decomposition products of cytolyzed cells will bring comfort to those who believe that ectoderm must be acted upon by an external agent before it will differentiate into neural epithelium. This suggestion, however, will require confirmation before it gains general acceptance.

Contact guidance is now recognized as the potent directive force by which a growing nerve fiber reaches its final destination (100). Further studies by Taylor (101) under the direction of Weiss bring evidence that individual fibers select the surfaces over which

they grow, for in the absence of ventral root fibers those whose cell bodies are in the spinal ganglia do not develop connections with muscles, though a typical pattern of cutaneous nerves is produced. Apparently the motor nerve which normally develops first in ontogeny provides a suitable surface upon which the sensory fibers advance into the musculature, for typical muscular nerves develop in the absence of dorsal root fibers. There are indications from the experiments of Yntema (102) that the neural crest cells play a role in assisting motor fibers toward their final destination for when the migration of the first sheath cells into the limb is prevented by the removal of the neural crest, the motor system fails to complete the innervation of the limb and to supply all the muscles.

Our understanding of the manner in which the number of sensory and motor neurons in the central nervous system is adjusted to the peripheral load which their peripheral processes supply has been extended and clarified, largely as a result of the observations of Hamburger and his pupils (103, 104, 105). The experimental findings now indicate that in all tetrapods the number of motor neurons in the cord segments supplying a limb bears a quantitative relationship to the area supplied. Likewise the number of sensory neurons corresponds to the peripheral load. The adjustment is wrought even though the peripheral field is provided by tissue of another species, for Bueker (106) describes an increase in the number of motor cells in the lumbosacral cord of a guinea hen provided with a field of chick mesoderm.

Of the central processes, cell multiplication, cell migration, and cell differentiation, through which the peripheral field might control the final number of neurons, Hamburger & Keefe (104) have eliminated the first. Cell counts indicate that the total number of cells in the brachial segments is not altered by the early removal of the wing bud. There is, however, a reduction in the proportion of the total number which differentiate into motor cells. No experimental data are at hand which would permit an elimination of one or the other of the remaining possible mechanisms. However, indirect evidence has accumulated from studies on the normal development of the cord (107) which favors the possibility that the periphery controls the number of motor neurons in the brachial segments by regulating the number which differentiate from a large supply of indifferent or undifferentiated cells.

Levi-Montalcini & Levi (108) in a paper which has only recently become available in this country, though it was published in 1942, have analyzed the mechanism by which the peripheral field exercises its control over the number of ganglion cells. In a series of chick embryos ranging between four and twenty days old, from which a limb bud had been removed at the end of the third day of incubation, the authors compared the numbers of undifferentiated and differentiated cells—as revealed by silver impregnation—on the side of the operation and the control. The number of undifferentiated cells was similar on both sides at all ages, but a smaller number of differentiated cells was found on the side of the amputation than on the control. The reduction in the number of differentiated neurons on the side of the amputation is due to a widespread atrophy of cells which reach that stage of development. The differentiated cells which degenerate are in all probability those individuals that fail to make appropriate connections with peripheral structures; hence the adjustment between ganglion and field appears to be achieved by a degeneration of the neurons which differentiate in excess of requirements, a possibility which is in complete harmony with observations on the histogenesis of the normal spinal ganglion (109). If these results are confirmed it would appear that the adjustment of the number of sensory neurons is wrought by mechanisms other than those which adjust the motor.

The mechanisms concerned in the finer differentiation of the internuncial and sensory systems remain obscure. The observation of Moyer (110) that the brachial cord of *Amblystoma*, when substituted for more caudal regions in the neuraxis, does not differentiate central mechanisms which permit coordinate movements of a limb supplied by its sensory and motor fibers, suggests that descending pathways which terminate in more anterior segments are essential to the normal differentiation of the brachial cord segments. But before the ability or the failure of any transplanted part of the nervous system to function can be analyzed further it will be necessary to study the finer differentiation of the transplant as revealed by silver impregnation methods. The gross adjustments (111) which transplants of the cord or the medulla make, as seen in hemotoxylin preparations, are but manifestations of the plasticity or rigidity of the proliferation phase of the development of the nervous system, in particular of the neuroglial elements. Per-

haps the time is at hand for an intensive study of the differentiation phase of the amphibian nervous system after the manner of the studies of Rhines (112, 113) and Piatt (114, 115). Specifically, Rhines finds that the ventral longitudinal tracts are not essential to the formation of commissures as earlier studies on Mauthner's cell appeared to indicate (116). Further evidence in this direction has been furnished by Piatt (114, 115) whose observations indicate that the shape of the neural tube may play an important role in directing the course of growing axons.

Functional development.—Interest in the functional development of the nervous system continues to advance along two main lines, one directed toward solution of the behavior problem and the other toward elucidation of the functions of the mature nervous system. The central problem confronting those interested in the genesis and development of overt behavior, i.e., does behavior result from the integration of simple reflexes or conversely by the segregation of isolated reflexes from a mass response, is the subject of an excellent review by Hooker (117) which contains a detailed account of his own investigations on the behavior of the human fetus. Hooker concludes that his own studies support the second alternative stated above and originally set forth by Coghill in 1929. This conclusion derived support from the recent histogenic studies of Humphrey (118) and of Youngstrom (119) on the early human cord. In these two studies a system of neurons is described which resembles the Rohon-Beard cells of the early amphibian cord. If these neurons form a functional system they might provide the structural basis for a total response in the human embryo similar to that which Coghill described for *Amblystoma*.

Further evidence to support the view that behavior develops by segregation is to be found in a study of flexor spasms and mass reflexes made by Coghill some years ago but only recently published posthumously (120). The assumption that the flexion reflex is the most primitive, that is to say the first to appear in mammalian ontogeny, must be accepted if the evidence is to furnish support for Coghill's views. This assumption will not pass unchallenged, for Windle and his collaborators have provided evidence, both histological and physiological (see 121), that the first limb reflexes are mediated by sensory fibers which end directly upon the ventral horn cells. On the basis of the recent studies of Lloyd (122) on the adult cord it appears fairly certain that these direct sensory fibers are proprioceptors and not exteroceptors.

Evidence has accumulated which indicates that the suppression of spinal activity, first observed to occur in sheep fetuses about mid term (123), may be a general phenomenon, for similar stages in which suppression occurs have been described in the human (124) and in the frog (125). The experimental findings indicate that in the sheep as well as in the frog the suppression is wrought by cells that lie in the anterior portion of the hind brain and which act upon spinal centers. The labyrinth is almost certainly involved. Later in the development of the frog the midbrain tends to counteract the inhibitory action of the hind brain.

The possibility that the very earliest movements of vertebrates are myogenic or neurogenic as opposed to reflexogenic continues to complicate analysis of the very earliest movements, in terms of the behavior problem. Observations on the cholinesterase content of *Fundulus* embryos, before and after inhibition of the esterase by eserine, have led Sawyer (126) to conclude that in this form the first movements are myogenic; at a later stage the movements are neurogenic, i.e., the result of the direct activation of internuncial or motor cells within the nervous system. Finally the central nervous system is activated through the sensory system and reflexogenic movements make their appearance.

The existence of a myogenic stage of activity in the development of the frog remains in doubt but there appears to be a neurogenic component (127) which is responsible for the spontaneous activity. The amount of spontaneous activity depends upon some internal stimulant the nature of which remains obscure, though it appears to be associated in some way with the yolk, for removal of the yolk doubles the spontaneous activity of decapitated larvae.

Quite apart from its contribution to the behavior problem the study of the function of the developing nervous system has added a third to the two classical methods of investigation of the nervous system, i.e., extirpation and stimulation. The possibilities of the method have been fully exploited in a beautifully executed research by Dr. Marion Hines on the development of motor control by the higher centers as seen in fetal and infant monkeys (128).

Analysis of their posture and progression reveals that in the development from infant to adult patterns the differential distribution of tone in the somatic musculature passes through these phases: (*a*) tonic innervation of flexors and related muscle groups, (*b*) spasticity and initiation of spontaneous movements proximally, and (*c*) the maturation of fixation and the dominance of

discrete movements of distal muscles. These three phases of activity are related respectively to the immaturity of areas 4 and 6, to the partial development of the pyramidal tract and the incomplete development of the anterior border of area 4 and, finally, to the maturation of the pyramidal tract and those extrapyramidal projection systems which originate, in part at least, in the frontal agranular area of the cortex. This functional expansion of the cortex appears to go hand in hand with a decline in its plasticity as judged by a decrease, as age advances, in the ability of infant and young monkeys to readjust their motor behavior after cortical extirpations (129, 130).

Observations upon the functional development of the visceromotor system have not kept pace with those on the somatic motor. Recently, however, the functional development of the vasomotor center has been followed in dogs (131) and the development of homeothermy has been studied in rats (132). Shivering and other muscular reflexes which tend to increase the internal temperature appear in the rat about nine to twelve days after birth, though homeothermy is not completely established until weaning time approaches.

The view that a nerve fiber does not conduct until it develops a myelin sheath has been steadily losing ground for the past ten years. Its death blow has finally been struck by the studies of Uett *et al.* (133), who have demonstrated that myelinization of the fibers of the corpus callosum and of the corticopontocerebellar system is not essential for the conduction of nerve impulses.

The nervous system at birth.—During early labor and its passage through the birth canal the mammalian fetus is subjected to varying degrees of asphyxia. The resistance of the fetus to asphyxiation determines its ability to survive and the nature of the damage caused in the central nervous system by the asphyxia has an important bearing upon the desirability of resuscitating severely asphyxiated infants at birth. Recent studies confirm the older observations of Bert (134) and of Edwards (135) which indicate that the resistance of the nervous system to anoxia is related to its stage of maturity. When placed in nitrogen immediately following birth at term rabbits and dogs continued breathing for thirty-one minutes; guinea pigs for only six; whereas rabbits delivered operatively at the onset of twenty-nine days continued breathing forty-four minutes in nitrogen (136). Rabbits retained in the uterus three

days past term ceased breathing in nitrogen in seventeen minutes which corresponds to the survival time of rabbits suckled three days following birth at term. Other things being equal respiratory movements continue longer in newly born rabbits asphyxiated by tracheal ligation than in individuals allowed to breathe nitrogen. The loss of the carbon dioxide appears to remove a potent stimulus to respiration even in animals so immature (137).

The central nervous system of the guinea pig is relatively mature at birth and appears to suffer irreparable damage if the new born individuals are asphyxiated and resuscitated (138, 139). The thalamus and the geniculate bodies are damaged more consistently than other parts of the brain but damage may occur elsewhere, for example in the cortex. These cytopathological changes are bilateral. Correlated with these structural abnormalities the animal exhibits motor and sensory defects. These defects have been shown to affect the ability of the guinea pigs to learn and remember a simple alternation problem four to six weeks later (140).

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WATER METABOLISM

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The literature of the current year contains an unusually large number of reports dealing with the special problems which have arisen from the necessities of war waged on a global scale. Significant additions have been made to our knowledge regarding the disturbances in fluid balance which result from such conditions as (*a*) extensive burns, (*b*) severe hemorrhage, (*c*) traumatic shock, (*d*) water and salt deprivation, and (*e*) exposure to extreme changes in environmental temperature and humidity. These receive special attention in the present review. Related topics, such as blood substitutes, renal secretion, and the special roles of proteins, electrolytes, and endocrine secretions, are dealt with as they relate to water metabolism. The general problem has been considered in two previous volumes of this publication (1, 2).

Water Deprivation and Dehydration

Much of the older literature dealing with water deprivation has emphasized the effects of salt deficiency, because the usual situation in clinical medicine in which the subject is deprived of water is one of fasting or one in which the salt intake is deficient. Warfare on sea or land not infrequently subjects men to a shortage of drinking water while food is plentiful. Studies (3) have been made on men under conditions simulating the latter situation, in that they abstained from drinking water for three or four days while taking a "dry" diet which was adequate in protein, salt, and calories. There was no reduction in total plasma volume. The sodium of the serum rose while the potassium fell. The amount of urea produced by the body during the period of dehydration increased. The excretion of minerals did not keep pace with that of water, and the osmotic pressure of the plasma and of the whole body rose. This increase in osmotic pressure in dehydration may be the cause of death. Some potassium was lost from the cells, which contributed water to the extracellular compartment. The same authors (4) confirmed the findings of previous investigators (5) to the effect that the body may lose as much as 10 per cent of its weight from water deprivation without any appreciable reduction in blood

volume. No significant reduction in blood pressure or glomerular filtration rate is demonstrable during dehydration produced in this manner. Changes which characterize the urine of dehydration are due, therefore, to tubular activity alone. The effect of varying salt intake during water deprivation was found to be that of increased plasma, which always led to a rise in urine volume, the extra water coming from tissue fluids (6). On rehydration in stages, the subjects of the latter study who had been deprived of water for some days on a diet containing five to fifteen grams of sodium chloride, showed a fall in urine volume when given somewhat less water than the amount of body weight lost. The amount passed in the first twenty-four hours of rehydration was always smaller than it had been during the days of dehydration. Accompanying changes were a fall in the percentage of chloride excreted and an increase in the percentage of urea. The latter was associated with a fall in serum urea. The authors considered that the reduced output of water and increased percentage of urea in the urine were both due to the fall in excretion of sodium chloride. Such a fall would certainly make for a diminution in urine volume. So much less salt presented itself for excretion that the percentage of chloride in the urine fell. This, the authors assume, allowed the kidneys to raise the percentage of urea.

The authors of this report are not in agreement with the conclusion of others (7) that beneficial effects are derived from drinking sea water under conditions likely to be encountered by men cast adrift at sea with little salt and insufficient calories. The supposedly beneficial effects, they think, can only be observed when the diet contains very little salt and when the intake of sea water is very sharply limited. Under the conditions of privation referred to by the latter authors (7), it was found that the urine volume did not fall after the first day on this limited regimen. Drinking up to 400 cc. of sea water (12 to 14 gm. of salt) increased the volume of urine, but not by more than, and often less than, the volume of sea water taken. All of the extra sodium chloride was excreted. The increased amount of water excreted improved the urea clearances and the extra water to drink, even though highly salted, had a good psychological effect. It is difficult to see, however, how a strongly hypertonic solution can possibly benefit a man who is already suffering from a water deficit. The extra salt can be excreted only at the expense of a further rise in the osmotic pressure

of the body fluids. In another study on the response to drinking sea water, it was found in rats that the inclination and ability to ingest and metabolize it varied among individuals (8). On the whole, the animals losing the same amount of body water survived slightly longer when allowed to drink sea water than when denied all water. The concentration of chloride in the urine of some individual rats was greater than that in sea water. The rats gained water from ingestion of sea water and subsequent excretion of its salts more slowly than they lost it by evaporation. However, half strength sea water or an equivalent solution of sodium chloride allowed indefinite maintenance of body weight in rats with augmented turnovers of water and salt. Maintenance of water content was not favored by progressive increases in the salt concentration of drinking water. Recovery from dehydration as a result of previous water privation did not occur when sea water or an equivalent concentration of sodium chloride was allowed. When fresh water was given, the corresponding recovery required several days' time. Fasting men allowed 1200 cc. of drinking water daily were found to suffer a net loss of approximately two liters of extracellular fluid in six days (9). This amount was reduced slightly when 4.5 gm. of sodium chloride was given. When instead of salt, 100 gm. of glucose was given daily, the loss was reduced to one liter and when both glucose and salt were given, there was a net gain for the period of between 300 and 400 cc. of extracellular fluid.

A peculiar type of dehydration was produced by administration of ammonium chloride (9 gm. daily) to human subjects on a low-salt diet (10). This procedure resulted in a reduction in plasma volume greater than that indicated by the rises in serum protein and hematocrit value. In spite of an initial water loss equivalent to between 3 and 4 per cent of the body weight, a secondary rise in plasma volume toward the normal level occurred subsequently while the regimen was still being continued. Prolonged water deprivation and starvation in the dog has been shown to result in the sacrifice by the organism of more potassium than that derived from the breakdown of tissue without a comparable sacrifice of sodium, indicating an exaggerated loss of intracellular and a minimal loss of extracellular water (11, 12). A similar effect has been produced by injection of various hypertonic solutions. It may be stated as a generalization that release of potassium from the intact cell and its renal excretion is a response to any severe depletion of

water. Death due to injection of excessive amounts of hypertonic saline solution has been shown to be of the respiratory rather than of the circulatory type of failure (13). Circulatory embarrassment is more likely to occur under the reverse conditions, namely, after depletion of extracellular salt and water, but the severity of the circulatory impairment cannot be attributed wholly to contraction in the extracellular volume. It has been demonstrated by studies on dehydration with and without salt loss that alterations in plasma volume do not always parallel those in extracellular fluid volume (14).

Water and Electrolyte Exchanges as Influenced by Environmental Conditions

Interest in the problem of man's acclimatization to heat has been further stimulated by the necessities of military action in hot desert and tropical climates. The physiological adjustments and their mechanisms are still but partially understood. Most investigators agree, however, that men working in hot environments maintain greater blood and interstitial fluid volumes than the same men have in cold climates (15). A temporary increase in resting cardiac output and increased peripheral circulation have been recorded (16). The sweat output is greater under given conditions in acclimatized men than in the same men before acclimatization, and the sodium chloride concentration of sweat is decreased by 50 per cent after a period of adjustment to work in a hot climate (17). More recently, it was reported that men, who developed symptoms of heat exhaustion at first after walking a treadmill for one to one and a half hours in a room where desert conditions were simulated, were able to carry on this same activity with comfort and ease after a few days of acclimatization (18). This change was accompanied by an increase in sensible sweating. The capacity for sweating in harder work than that of the standard experiment likewise increased. It would be of interest to know whether or not the insensible water loss varies with acclimatization to work in the heat. Thirst has been found to be an inadequate guide as to the amount of fluid required for work in hot climates (19). Not one of forty-eight men so exposed drank enough water voluntarily to replace that lost in the sweat, all developing a water deficiency under such conditions. Work performance was significantly better in men taking sufficient fluid to replace fully the amounts lost than in those tak-

ing it according to the dictates of thirst alone. In tests on the effects of water restriction in heat (120°F. with 15 to 25 per cent relative humidity) it was found that progressive restriction was much better tolerated than sudden restriction by both acclimatized and unacclimatized men. However, the rate of acclimatization was uninfluenced by the level of water intake. Fully acclimatized young men on a complete diet, performing intermittent work at an environmental temperature of 100°F. and relative humidity of 35 to 45 per cent, showed their best performance when the water lost in the sweat was replaced hourly by plain drinking water (20). So long as the subjects' regular meals contained adequate salt, no advantage was gained by adding either salt or glucose to the hourly supply of water. Exhaustion of dehydration was found to occur within two hours or less under the same conditions if no water was drunk, because sweating was about as profuse whether water was drunk or not. Blood volume, cardiac output, and velocity of blood flow are known to be greatly reduced under such degrees of dehydration. It has been shown (21) that intravenous infusions of sufficient fluid for rehydration increase the cardiac output and stroke volume markedly in dehydrated patients, but only slightly, if at all, in normally hydrated subjects. Rapid infusion of large amounts of physiological saline solution in normal dogs, however, has been found (22) to produce not only increase in the plasma volume and cardiac output, but increase also in heart rate, oxygen consumption, and peripheral congestion, with development of gallop rhythm, systolic murmur, and finally congestive heart failure.

In a study of the effects of sodium chloride intake on work performance of forty-nine men during exposure to dry heat (120°F.) and experimental heat exhaustion, it was found (23) that men on low intake (about 6 gm. daily) suffered an average net deficit of 13 gm. of salt for three days in the heat. Those taking 15 gm. or more daily showed little or no deficit. The volume of sweat lost varied between five and eight liters daily, amounts similar to those reported by earlier observers (24) for men working in the hot desert. Men receiving the lower allowance of salt lost an average of 8.39 gm. of sodium chloride on the first day, this fact indicating a net loss of 1.74 liters of extracellular water or 10.3 per cent of the total volume of 16.87 liters, the average found in 10 normal subjects (25). Men on the low-salt intake lost more than twice as much body weight, drank less water, and sweated less than those

on "moderate" intake (15 gm.). They had higher pulse rates and rectal temperatures and poorer cardiovascular adjustments than those on the latter intake. There was no advantage, however, according to all measurements made, in the subject's taking 30 gm. of salt daily. Dehydration, nausea, vomiting, tachycardia, hypotension, vertigo, and collapse occurred in 25 per cent of the men on low sodium chloride intake and in 2.5 per cent only of those on the moderate intake. Although hypochloremia was found in many of the men, "heat cramps" in the muscles did not occur.

In a study of the factors influencing chloride concentration in human sweat, other workers (26) investigated the variations under special conditions in a number of young men marching for some hours in temperatures ranging between 100° and 120°F. with relative humidity of 30 per cent and in temperatures between 80° and 95° with a humidity of 85 per cent. They confirmed the commonly held views that sweat chloride (*a*) increases as work is prolonged; (*b*) varies between individuals; (*c*) varies inversely as the supply of drinking water; and (*d*) increases as the rate of sweating increases. In addition, they found that the sweat chloride increases with increasing body temperature and with increasing local skin temperature, but decreases more after ingestion of saline solution than after an equal volume of water and within wide limits is independent of plasma chloride, plasma protein, and physical fitness. A new interpretation is presented by the authors concerning sweat chloride during acclimatization. It was shown experimentally that, if the rectal and skin temperatures were the same, the sweat chloride was the same before and after acclimatization, indicating that the lowering of body temperature during the process is responsible for the variation in sweat chloride.

An interesting new clinical entity involving failure of the sweat mechanism (thermogenic anhidrosis) has been described in eight patients from a group of soldiers actively engaged in military training in the American desert area (27). The picture differs radically from that of ordinary heat cramps, heat exhaustion, or heat stroke. Its onset is sudden with apparently complete cessation of sweating confined to the body below the neck. It is usually preceded by a distinct period of profuse outpouring of sweat from a few days up to several weeks in duration. While beads of sweat appear over the face and neck, the skin below this level is warm and dry and presents a goose-flesh appearance. Subjectively there is

sudden onset of generalized weakness, an "all-gone" feeling, dizziness, headache, and shakiness. Salt gives no relief. Removal from the heat is the only known procedure for correcting and preventing recurrences in subjects who are known to react in this manner. Similar signs and symptoms have been observed by others in some cases of collapse during exposure to artificial fever (28). A state resembling that of traumatic shock, with the pallor, cold extremities, high body temperature, absence of sweating and urinary excretion, and mania and unconsciousness is associated with dehydration of the blood plasma. The latter authors believe that this condition can be prevented by adequate water and salt administration. They found measurement of the specific gravity of the plasma to be the best means of determining the need for such fluid.

Measurements of the water exchanges in eighteen subjects spending the greater part of four days on pneumatic life rafts in the Gulf of Mexico, where climatic conditions were such as to cause the daily requirement of water to approach the maximum to be encountered on any ocean, showed the average daily evaporative loss of water to be 730 cc., an unusually low figure (29). It was concluded from these studies that, as long as physical exertion is minimal, sea sickness is not excessive, clothing is kept moist with sea water, and a light breeze blows, a supply of 500 to 1,000 cc. of water daily will prevent the occurrence of dehydration in semifasting survivors on lifeboats or rafts in the tropics. The effects on weight conservation of wearing wet clothing under conditions of high environmental temperatures, with varying levels of relative humidity and wind velocities, have been determined experimentally (30). The mean hourly weight conservation attributable to the wet clothing was found to be 174 gm. at rest and 309 gm. at work, when the temperature was 110°F., relative humidity below 25 per cent, and wind velocity 25 feet per minute. This effect was absent with relative humidities above 35 per cent. The average hourly weight conservation was 76 gm. at rest and 94 gm. at work with the air temperature at 77°F., the relative humidity 67 per cent, and the wind velocity 50 feet per minute. Rectal temperature was not affected by the wet clothing. However, the pulse rate was significantly slower. The subjects' preference for the wet garments was in general proportional to their weight conservation effect.

Variations in the rates of both insensible and sensible perspira-

tion over different areas of the body are not inconsiderable. In an extensive study of this aspect of the water balance problem involving seventeen different areas of skin of forty-six normal adults, it was found (31) that the most rapid rates of insensible water loss occurred over the hands, feet, forehead, and cheeks. The skin of the trunk, arms, and legs had relatively slow rates of insensible perspiration. There was great variability from subject to subject and in the same subject from time to time. Similarly great variations were found to occur in the rates of sensible sweating over different areas when subjects were exposed to a hot and humid environment. The areas showing the lowest rates of insensible water loss were found to have the highest rates of sensible sweating. The rate of water loss from the skin of a subject resting quietly in bed was not found to be materially increased when the temperature and relative humidity were increased from 75°F. and 50 per cent, respectively, to 95°F. and 75 per cent. When the temperature was further increased to 100°F., however, sweat was found literally to pour from the skin. The phenomenon of "cold" sweating, which is defined as the sweating which occurs without an adequate thermal stimulus, has been found (32) to be the most reliable and constant indication of the onset of motion sickness. Sweating occurred in healthy young men subjected to motion involving changing linear and centrifugal acceleration in spite of lowered body temperature produced by increased wind velocity in the atmosphere. The rate of the cold sweating, measured by means of a galvanometric device to indicate time of onset of perspiration and a calcium chloride plaque to collect it, was found to vary between 0.08 and 2.2 mg. per square cm. per minute. No useful physiological purpose was found to be served by cold sweating.

Cold environments.—In contrast with the effects of a hot environment on water metabolism, those of hypothermia appear to be conservative (33, 34). Exposure to cold sufficient to lower the body temperature to between 16° and 23°C. with retention of protective reflexes was found to cause an increase in intracellular water throughout the body. When the central nervous system became so chilled as to cause general neuromuscular depression, however, the effect on the hypothalamus was to abolish the reflex responses to cold, which produced a reversal of the water shift, causing an increase in extracellular fluid. Subcutaneous edema and hydration of the blood (as determined by specific gravity changes) developed,

and were still further augmented on rewarming the animal to a body temperature of 30°C. In a subsequent study (35) on the effects of a series of drugs on the changes produced by hypothermia, the hydremia was discovered to be due to passage of water from the cells to the blood. Hydration of the blood was still further increased as the subcutaneous edema disappeared upon rewarming. Betatetrahydronaphthalamine hydrochloride was superior to other drugs in causing disappearance of the edema. Ephedrine reduced the edema earliest in the rewarming period.

Renal Excretion of Water and Electrolytes

Effects of low barometric pressure and anoxia.—That secretion of urine is affected significantly by low barometric pressures (anoxic anoxia) has been demonstrated by a number of different observers (36, 37). Dogs anesthetized with barbiturates developed a distinct oliguria when made to breathe atmospheres with reduced oxygen tensions corresponding with altitudes of 14,000 to 30,000 feet. However, unanesthetized dogs showed polyuria instead of oliguria under low oxygen tensions (38, 39). Urinary output in normal men was found to increase between 100 and 300 per cent when they were subjected to a simulated altitude of 12,000 feet for four or seven hours daily (40). Polyuria was found to occur invariably in rats as a result of exposure to atmospheres above 15,000 feet (41). At 30,000 feet, the effect was more marked than at 15,000 feet. Cold (10°C) intensified the polyuria, while heat (30°C.) lessened it. The polyuria increased with increased water load. Phenolsulphonephthalein excretion was not affected by the low pressure conditions. Anemic anoxia produced by carbon monoxide had the opposite effect of reducing both urine volume and dye excretion. Posterior pituitary extract inhibited or reversed the polyuria of high altitudes. It was earlier observed that exposure of rats to low barometric pressures resulted in excessive weight loss without thirst (42). The main factor was considered to be anoxia, because such loss was prevented by giving oxygen instead of air to breathe at low pressures. The loss occurred at high pressures when the animals were subjected to a gaseous mixture containing 10.5 per cent oxygen and 89.5 per cent nitrogen. An analysis of this weight loss in subsequent experiments (43) showed it to be due to an increase in insensible perspiration.

Renal hypertension.—A 75 per cent increase in water consump-

tion was observed in rats made hypertensive by experimentally produced ischemia (44). When but one kidney was made ischemic, the normal kidney frequently exerted a compensatory influence which masked the effects. The appearance or exacerbation of the disturbances in water metabolism upon removal of the normal kidney, on the one hand, and the elimination or mitigation of symptoms upon removal of the ischemic kidney on the other, support the view that the changes observed could not have been due to passive elimination of kidney tissue by the ischemia, but to active malfunction of the renal and especially the tubular mechanism upon withdrawal of oxygen. On the basis of these observations, the view was advanced that polyuria under these conditions is a primary sequel of ischemia rather than being secondary to the intra- and extrarenal effects of hypertension. Analyses of the skeletal muscles of dogs with experimental renal ischemia and hypertension showed the total sodium and chloride content to be increased and the potassium to be decreased (45). There was a redistribution of muscle water involving a shift from the intracellular to the extracellular phase. The calculated mean values per kg. of muscle were: extracellular phase, 254 ± 54 gm.; intracellular phase 532 ± 47 gm.; and total solids, 214 ± 8 gm. This indicates an increase of 65 per cent in the extracellular phase as compared with that in normal dog muscle. After a massive intravenous infusion of physiological saline solution, half of the total increase in muscle water was contained in the cells and the other half was extracellular. No significant difference was found in the amount of antidiurectic principle in the urines of renal hypertensive dogs and in those from normal dogs, either during normal hydration or during dehydration (46). The amount is increased in both during dehydration. The results do not support, nor do they rule out, the possibility that the activity of the posterior lobe of the pituitary is altered in experimental renal hypertension.

Diabetes insipidus.—The only demonstrable abnormality in the renal function of animals with experimental diabetes insipidus is the excessive excretion of water (47, 48). Demonstration of the existence of this peculiar disability has been proposed as a reliable method for differentiating true diabetes inspidus from several other conditions characterized by polyuria and polydypsia (49). If the specific gravity of the urine of a patient suspected of diabetes insipidus is found to be above 1.010 after he has refrained from

drinking water to the point of discomfort, it is almost certain that he does not have diabetes insipidus. The mechanism of this abnormality has been further investigated (50). In an experimental study on the behavior of chloride in the kidney of the normal dog, no apparent limit was found to the amount of chloride excreted per minute or to its concentration in the urine and no general relationship between chloride excretion and plasma chloride concentration was seen. Nor was there a tubular reabsorption maximum for chloride, at least up to a fourfold increase in glomerular filtration. If, however, the quantity of chloride reabsorbed was compared with the quantity of water reabsorbed simultaneously, a definite and constant relationship was found. A comparison of the chloride to water ratio in the reabsorbate with the chloride concentration of the plasma was found to be a useful expression of the reabsorptive process. The chloride to water ratio of absorbate was decreased with lowering of plasma chloride concentration and increased elevation of the latter. This relationship was very inconstant in dogs with active diabetes insipidus. Since pitressin corrected this inconstancy without direct effect on chloride, it was concluded that this antidiuretic hormone controls the relationship between reabsorption of water and chloride by regulating water reabsorption alone. Conceding that electrolytes have a fairly definite excretion threshold, Barclay & Cook (51) have pointed out that this threshold, excepting under rigidly standard conditions, varies from time to time, probably under hormonal influence. Excretion of electrolytes, like that of water, is practically independent of rate of glomerular filtration, but is regulated by tubular reabsorption. Since infusion of hypertonic saline greatly increases urinary excretion of pituitrin while hypotonic saline or glucose solution or pure water inhibits the secretion (52), it has been postulated that for the regulation of water exchange there is a system, including the hypothalamicohypophyseal mechanism, which controls the secretion of pituitrin through its sensitivity to changes in the salt content of the blood and thereby the concentration in which salt is reabsorbed by the renal tubules. An interesting form of congenital diabetes insipidus, occurring in several members of the same family but without known cause, has been described (53). The extreme polyuria and polydypsia are uninfluenced by pitressin, although the latter causes an increased excretion of sodium. Manitol and urea clearances and other renal function

tests are normal during periods of complete hydration, but the power to concentrate urine is extremely defective. Restriction of water intake for eight or ten hours causes high fever, increased skin resistance, and a marked increase in the concentration of sodium and chloride in the plasma (e.g., Na, 178 and Cl, 128 m.eq. per l.). When water intake is unrestricted, drinking is almost continuous and the sodium and chloride of the plasma fall distinctly below normal values.

A study on the effects of dietary changes upon urine volume and renal function in experimental diabetes insipidus showed that in both dogs and cats with diabetes insipidus the polyuria varies directly with the sum of the osmotic activities of the sodium chloride and nitrogeneous waste products in the urine (54). Nitrogen partition determinations showed no evidence of any abnormality in nitrogen metabolism in diabetes insipidus. Creatinine clearance studies showed that the changes in urine flow accompanying variations in protein intake extended into the post-absorptive period, after glomerular filtration had returned to the level observed post-absorptively on a control diet. Post-absorptive tubular reabsorption of water, however, was greater on a low-protein diet and less on a high-protein diet than in the controls. Observations made by the same workers (55) on the effects of administering 2.5 to 10 mg. of desoxycorticosterone acetate daily to dogs with diabetes inspidus showed the polyuria already existing to be greatly increased. Similar injections in a normal dog caused mild polyuria. Pitressin only partially controlled the polyuria due to desoxycorticosterone acetate, even when given in a dosage several times that required to render a dog with diabetes insipidus nonpolyuric. Reduction of protein intake reduced desoxycorticosterone polyuria, but not so strikingly as it did the polyuria of diabetes insipidus. Increased protein intake markedly increased the polyuria. Creatinine clearance studies showed that both in normal and diabetes insipidus dogs desoxycorticosterone reduced tubular reabsorption of water. Doses as large as 10 mg. daily also increased glomerular filtration, but smaller doses had little effect. In contrast to these effects in the dog, desoxycorticosterone acetate in doses as high as 30 mg. daily failed to increase the water exchange in normal cats. In cats with diabetes insipidus, such injections increased neither the polyuria nor the dosage of pitressin required to relieve it. Normal rats given free access to both water and salt showed marked poly-

dypsia when injected with desoxycorticosterone acetate, whereas those deprived of salt showed no increased thirst (56). It was concluded, therefore, that the effect of the injected sterol was merely that of increasing appetite for salt, the polydypsia being a consequence of this rather than a manifestation of a primary effect on water metabolism. Thyroid administration exaggerates the polyuria in animals with diabetes insipidus (57 to 61), while thyroidectomy reduces the urine volume (57, 60, 62); cats as well as dogs are so affected. Since a high salt intake greatly increases the water exchange in diabetes insipidus (57, 63), the effect of thyroid feeding upon the excretion of sodium chloride in cats with diabetes insipidus was investigated (64). It was found that the increased output of urine was associated with a diminished chloride excretion. Normal animals showed the same chloride response to thyroid feeding, but without polyuria. Thyroidectomy affected the chloride excretion but little after the first day or two postoperatively. Thyroid feeding caused a net rise of about 12 per cent in urinary nitrogen excretion in normal cats and in those with diabetes insipidus. In an attempt to determine whether increased glomerular filtration or decreased tubular reabsorption is responsible for the exaggeration of polyuria, the effects of thyroid extract and pituitrin on the creatinine and chloride clearances were investigated in (*a*) normal dogs, (*b*) dogs with severe diabetes insipidus due to lesions of the hypothalamicohypophyseal system, and (*c*) dogs with latent diabetes insipidus (65). When given thyroid, dogs with severe diabetes insipidus (presumably without pituitrin secretion) showed little change in clearances, but in dogs with latent diabetes insipidus, in which the pituitrin secretion was just adequate for normal control, it produced the same effect as surgical excision of the hypophyseal remnant by elevating the threshold to pituitrin above its normal concentration in the blood. Thyroid appears to increase glomerular filtration and to diminish the effectiveness of pituitrin in controlling the renal tubular reabsorption. Following subsidence of the initial marked polyuria, desoxycorticosterone acetate given to completely hypophysectomized rats in one mg. daily doses elevated the total water exchange but not to levels characteristic of diabetes insipidus (66). Whole extract of adrenal cortex was without effect. Thyroid feeding in doses that restored oxygen consumption to normal elevated the water intake slightly, but did not raise the urine output. It is assumed by the authors

that the diuretic effects of thyroid hormone under other circumstances in the rat must depend upon the presence of the anterior pituitary.

Renal function in young infants has been further shown to be immature in its development, as determined by the inability of babies to maintain a normal internal environment under conditions which would not be considered unfavorable in adult life (67). This finding confirms and extends earlier observations (68). The serum of infants tends to show extreme variations from normal as a result of vomiting, diarrhea, or the injudicious use of saline therapy. Doses of posterior pituitary extract which produce pronounced inhibition of water diuresis in adult subjects was found to have a very slight and only a fleeting effect on the urinary concentration of newborn infants excreting a markedly dilute urine, which fact indicates a low sensitivity of the renal tubules to this antidiuretic hormone. A peculiar new form of intestinal alkalosis and dehydration in infants, resulting from extensive losses of water and chloride by way of the intestinal tract, has been described independently by two different workers (69, 70). The chloride and potassium of the plasma were decreased, while the pH and carbon dioxide content were increased. The urinary excretion of chloride was minimal. Whether a congenital aberrance of renal function is involved or not is unknown.

A special technique for studying the relative retentions of constantly infused solutes and water has been described and theoretical aspects of the isorrheic state (constant urine flow or solute excretion with constant infusion rate) developed on the basis of experimental studies on the dog (71). The velocity constants of excretion or rate of excretion per unit load of water, chloride, and urea are ascertained. They can be used to characterize those critical concentrations of infusion fluid and urine at which neither solute nor water is retained from an infusion, relative to one another. For chloride, expressed as the sodium salt, these concentrations were found to be approximately 6 and 17 mg. per cc. For urea the only such concentration was approximately 35 mg. per cc., when the simultaneously infused chloride was less than 17 mg. per cc. Rehberg's concept of threshold concentrations for ions like chloride is extended by this new concept. The urea clearance in man rises continuously with all diureses in renal disease as well as in health. A valid objection has been raised (72) against the current practice of expressing the clearance of a subject with kidney dis-

ease in per cent of normal clearance, on the ground that certain factors previously assumed to be constant in both situations actually change in renal disease. The fallacy of comparing the specific gravity of the urine in concentration tests for renal function determined at small urine flows with the clearance of urea at any urine flow is also pointed out. The equation, $C=A(1-e^{-kv})+bv$, in which C stands for the clearance, v for diuresis, A, k, and b are constants, and e is the base of the natural logarithms, is thought to be an adequate representation of the relations between the clearance and diuresis at all levels of the latter.

The advent of sulfonamide drug therapy has presented new problems of renal excretion in that excessive concentration of these agents in the urinary tubules not infrequently results in the formation of crystals which obstruct the flow of urine, producing fatal uremia. Normal rats, given sodium sulfadiazine intraperitoneally in doses of 0.15 gm. per 100 gm. of body weight in a 5 per cent solution, develop such renal obstruction within a few hours and 70 to 80 per cent succumb to this complication. In a recent study of the therapeutic effects of various fluids administered by stomach tube to sulfadiazine-treated rats at the rate of 3 cc. per 100 gm. of body weight twice daily, significant results were obtained (73). Although all animals had free access to drinking water, the urine volumes and drug excretions were very low and the nonprotein nitrogen and drug levels in the blood were extremely high in the control animals and in those receiving (*a*) water alone, (*b*) 1.67 per cent ammonium chloride solution, or (*c*) 3.33 per cent sodium bicarbonate. The mortality in these groups varied between 80 and 100 per cent. In contrast, rats given a combination of the two latter solutions in equal volumes or a solution of 3.33 per cent sodium chloride showed much higher urine volumes with better drug excretion. None of the animals in these two groups died.

Water Content and Distribution

In the normal state, the water content of the body as a whole and that of the vital organs tends to remain fairly constant. The water percentage in tissues, its allocation between the several fluid compartments and the rates of turnover differ significantly with age, but, aside from such variations, wide deviations in water content or in the distribution or composition of the body fluids signify the existence of a pathological state.

Determination of the total body water in the living animal.— Presumably any nontoxic, nonmetabolizable, chemically inactive substance which would diffuse throughout the entire fluid mass of the body in uniform concentration would afford a means for making such measurements. In a recent study (74) on total water content and the magnitude of changes induced by various means, injected thiourea was found to be distributed through a volume of fluid which either approximates or slightly exceeds that assigned ordinarily to total body water. Changes measured by its use agreed with those determined by metabolic calculations within 4 per cent. Since water intake by mammals is a discontinuous process, while the output is continuous, water balance varies somewhat between drinks. To study the extent of such variations in relationship to controlling factors (75), a trained dog with exteriorized bladder was suspended from a Sauter balance in a stall with surrounding temperature of 22° to 26°C. and relative humidity of 30 to 50 per cent. Drinking water was kept in a can immediately in front of the animal. Insensible weight losses and urine excretion were measured every fifteen minutes. Under these standard conditions, the signal found to initiate water drinking was a loss of water equivalent to 0.5 per cent of the body weight. The amount drunk voluntarily at each draft was accurately proportioned to the body's deficit, though the absorption of water did not have time to occur before drinking ceased. Application of heat, which accelerated weight loss, made the animal drink more frequently but again after an interval corresponding to a weight loss of similar magnitude. The pattern of water drinking was modified by the taking of comparatively dry food at certain intervals. The dog drank after each feeding, even when the weight was increasing.

The normal distribution of water and electrolytes in the skin and other organs is still an open question. Recent measurements (76) showed figures for the skin of normal adult dogs as follows: total water, 708.3 ± 20.1 gm. and chloride, 86.7 ± 2.5; sodium, 96.5 ± 4.2; magnesium, 3.03 and potassium 22.4 ± 2.7 mM per kg. of fat-free tissue. Since the ratio of sodium to chloride in the skin was 1:11 instead of that found in an ultrafiltrate of the blood plasma taken at the same time, it was inferred that part of the chloride occurred within the cells. The intracellular space calculated from the assumption that all of the chloride is extracellular was too small if the potassium and magnesium of the skin are con-

sidered to be intracellular. Determinations of the water, nitrogen, and electrolyte contents of normal dog brain (77) showed the following mean values per kilogram for both cerebral hemispheres: water, 761 and nitrogen, 18.9 gm.; and chloride, 36.7 mM; sodium 51.0 mM; and magnesium, 5.6 mM with small standard deviations. Cerebellar tissue was found to contain nitrogen and electrolytes in approximately these concentrations, but the water content was significantly lower, 745 gm. per kg. Partition of brain water between intra- and extracellular compartments, on the basis of chloride and sodium content is not simple, as in the case of muscle. A considerable amount of the sodium in the brain is intracellular or is associated with myelin.

Evidence that the water content of the liver increases during the process of glycogenesis has again been obtained (78). Rats fed glucose for twelve hours following thirty-six to forty-eight hours of fasting showed a loss of non-glycogen solids with water storage. In thirty to forty-day-old chicks, fasting from fourteen to seventy-two hours produces a rise in blood sugar (79). Dehydration accentuated this rise. Insulin sensitivity of chicks was not increased by either fasting alone or fasting plus dehydration. The variability of blood glucose was increased by fasting but decreased by dehydration.

It has long been assumed that the large amounts of water and electrolytes lost by the diabetic in acidosis are derived from both the extracellular and intracellular compartments. In experiments on diabetic patients and pancreatectomized dogs it was found (80), however, that the water excreted actually comes from the intracellular compartment, the total amount in the circulating serum being increased. Administration of glucose to severely diabetic patients without ketosis led to a transfer into the circulating serum of water, sodium chloride, and glucose from the tissues. In pancreatectomized dogs with ketosis, there was observed a similar continued transfer. On the other hand, administration of insulin to diabetic patients was found to produce a reversal of these processes with transfer of water and electrolytes as well as glucose into the tissues. Administration of excessive amounts of water and sodium salts to diabetic patients with reduced potassium intake causes storage of glycogen (81). That water storage in the body is not a characteristic feature of the mechanism of carbohydrate-induced paralytic episodes in familial periodic paralysis, as claimed by some observers, has recently been demonstrated (82).

Alcohol was found to cause an increase in the extracellular water of fasting rats from 30.6 per cent of total body water to 33.6 per cent (83). In fed animals, the increase was from 31.6 per cent, in the controls, to 43.1 per cent in those given alcohol. Increases in the extracellular volume were shown to have been derived from the intracellular space. Thirst due to alcohol was not relieved by water in amounts equal to those lost in diuresis. In the frog, anesthesia (by alcohol or chloretone) produced an increase in body water in a manner similar to posterior pituitary gland extracts (84). When given together, alcohol and pituitrin produced increases in body weight equal to the sum of increases produced by the two. The hemodilution produced by barbiturate anesthesia (85) was partially reduced by superimposed ether anesthesia (86), which characteristically causes hemoconcentration (87). Pentobarbital anesthesia was found to cause increase in plasma protein concentration and at the same time a decrease in the hematocrit value in both dogs and cats.

Analyses of the tissues of thyroidectomized guinea pigs made exophthalmic by extracts of the anterior pituitary gland showed the hypertrophy of the orbital fat tissue to be due to a three-fold increase in total water rather than to an increase in fat (88). Most of the hypertrophy of extraocular muscles was likewise due to an increase in water content. Peritoneal fat showed some increase in water but less than the orbital tissue. No increase was found in the water content of a pooled sample of the skeletal muscles. The occurrence of edema in some patients suffering from severe vitamin-B deficiency ("wet" beri-beri) has long been regarded by some observers as evidence of a specific relationship of these vitamins to water metabolism. Determination of the water content of the whole body, the skin, and various parenchymatous organs of normal rats and of rats given the same diet minus vitamin-B complex, showed the latter to contain a higher percentage of water in the whole body but the same content in the abdominal organs, brain, and muscles (89). The difference was due entirely to the increase in the percentage of water in the skin, which was related entirely to loss of subcutaneous fat from failure to eat and not to the vitamin deficiency *per se*. When the two groups of animals were made to consume the same amounts of food and drink, there was no difference in the total water content.

In contrast to this negative effect of vitamin-B deficiency, ad-

renal gland deficiency has been found to cause a marked retention of water (90). After receiving 20 cc. of water per 100 gm. of body weight, adrenalectomized rats retained 12 cc. as compared with 2 cc. for a normal group. The average hematocrit readings and thiocyanate volumes in the adrenalectomized group were not significantly different from those of a group which received no water. The normal group, retaining but 2 cc. of water per 100 gm. of weight, showed a significant drop in their hematocrit readings. It was concluded that the extra water retained by the adrenalectomized rats was held in the intracellular compartment. The administration of desoxycorticosterone to four normal human subjects in doses of 10 mg. daily for five to fifteen days resulted in a considerable increase in plasma volume in all (91). The increase persisted throughout the period of injection, but fell to normal or slightly below within three days after its discontinuance. The magnitude of the changes in plasma volume was not significantly influenced by diet or supplementary salt administration. No demonstrable change was induced in the water content of the brain, liver, or skeletal muscles of normal rats receiving daily intramuscular injections of 1 mg. of desoxycorticosterone acetate for from seven to forty-one days, in spite of a reduction of approximately 20 per cent in the potassium content (92). The loss of intracellular potassium was compensated for in part by transfer of sodium into the cells. Desoxycorticosterone acetate was found to be less than one-tenth as efficient as whole cortical extract in protecting adrenalectomized rats against the collapse which follows intraperitoneal injection of isotonic glucose solution (93). The decreased ability of adrenalectomized rats to transfer water and electrolytes from the interstitial spaces into the peritoneal cavity by way of the blood stream could not be corrected by any therapy used. Likewise the initial hemoconcentration in the period of rapid water transfer to the peritoneal cavity could not be reduced to that characteristic of the intact rat. The effect of desoxycorticosterone acetate on water exchange has been reviewed elsewhere (94).

Fairly marked increases in the total water of the skin and in the extracellular water volume of normal rabbits followed the injection of estrogenic hormone in doses of 0.2 mg. daily for 3 weeks (95). Since such injections had previously been shown to increase the resistance of rabbits to dermal infection with vaccinia virus and to delay spread of inert particulate matter (India ink), these effects

were assumed to be the result of the increased water content of the skin. Intraperitoneal administration of saline solution, which also increased the water of the skin and subcutaneous tissues, was found to have effects similar to those of the estrogenic hormone.

Transfer of Water and Electrolytes through Membrane Barriers

Availability of heavy water (deuterium oxide) and radioactive elements has stimulated further investigations on this vitally important subject. Heavy water was found to pass to and from the guinea pig *in utero* with increased rapidity as gestation advanced (96). Its transfer across the placental barrier was found to be fifty times more rapid than that of radioactive sodium and five hundred times more rapid than the rate of its incorporation into the growing fetal tissues. In studies on the transfer of heavy water (97) and of radioactive sodium (98) across the blood-extravascular-fluid barrier, the same authors found that the amount of water relative to that of sodium transferred per minute was about twice that expected from their relative concentrations in the plasma. The amount of water transferred per minute was 146 per cent of the total plasma volume. Whereas radioactive sodium was found to be absorbed one hundred times faster per unit of surface area from the antrum than from the acid-secreting body of the dog's stomach (99), heavy water was found by the same workers to be absorbed at equal rates from pouches representing the two segments (100). Half of the deuterium oxide was absorbed in approximately twenty minutes. This transfer of water, while rapid, is apparently much slower than that into and out of the eye. One half of the aqueous humor was found by other workers (101) to be replaced every 2.7 minutes in rabbits and every seven minutes in monkeys. When a series of radioactive elements were injected intravenously, the levels of labeled bromide, sodium, and strontium tended to plateau after about one hour (102). Calculations at such levels indicated that the injected isotopes of sodium and bromide became exclusively and uniformly distributed throughout the extracellular fluid of the body. About 95 per cent of the radioactive potassium was excreted or passed into the intracellular phase in an hour. The rate of increase in concentration of the labeled ions in the cerebrospinal fluid followed the order $K > Na > Br > Rb > Sr > PO_4 > I$. The observed hindrance to the free passage of the ions from the plasma

to extracellular fluid of the nervous system and deviation from the Donnan law were interpreted as constituting evidence that exchange between the blood and brain occur by a special process of secretion and not by simple diffusion or ultrafiltration. The rate of entrance of radiosodium into the aqueous humor of the eye and the cerebrospinal fluid from the blood was studied as an approach to the problems of the mechanism of formation and the fate of these special fluids (103). In the anesthetized dog, the concentration of radiosodium in aqueous humor reached 75 per cent of the plasma level forty-five minutes after its intravenous injection, a much faster rate than previous studies would indicate. It was somewhat slower in unanesthetized animals. In anesthetized animals, the rate of approach to equilibrium between the plasma and the cisterna fluid was 25 to 40 per cent as great as in the case of aqueous humor.

Permeability of the capillaries was found to be greatly increased in myxedema, as determined by a special dermofluorometric technique, in which fluorescein is used as a test substance. The author (104) believes that the primary retention of fluid in the tissues and serous cavities, and the changes in the heart itself in myxedema are all due to this increased capillary permeability. Similar changes were found in nutritional edema but not in cardiac edema or in edema associated with liver cirrhosis. Thyroid replacement therapy caused a return to normal permeability and disappearance of the signs of myxedema.

Edema.—In a study (105, 106) on the influence of hypoproteinemic edema on intestinal absorption and motility, it was found that neither of these latter functions was disturbed as they are in certain other deficiency states. Galactose and aminoacetic acid were both absorbed and metabolized as well in the edematous as in the normal control dogs. Although the thiocyanate volume was measurably increased, there was no significant change in plasma volume associated with the edema produced by plasmapheresis. The specific dynamic action of protein was found to be slightly, and the basal metabolic rate markedly, reduced (by 40 per cent in some cases) in twenty human subjects suffering from protein starvation or nutritional edema. The reduced basal rate persisted for several months after disappearance of the edema. Severe undernutrition, involving the endocrine glands as well as other tissues, is probably responsible for this effect. In that form of hypoproteinemic edema

resulting from impaired ability of the liver to fabricate serum proteins, the general nutrition may remain unimpaired and the energy metabolism may be well within the normal range (107). The special role of the skin and corneal layer in restraining edema formation and preventing loss of body fluid has been emphasized (108). The fluid dynamics may be quite different in chronic congestive heart failure and in acute heart failure. In a study on the development of edema in certain patients with congestive failure, it was found that the primary effect of decreased cardiac output was impairment of the ability of the kidneys to excrete salt and water (109). This latter disability was not due to congestion of the kidneys from increased venous pressure, as previously thought, because salt and water retention appeared before such increase occurred. The increase in plasma and interstitial fluid volume was regarded as an effect of the salt and water retention. The resulting decrease in concentration of circulating proteins appeared to serve as a stimulus to accelerated protein production, causing an increased plasma volume without a marked lowering of the colloidal osmotic pressure. The rise in venous pressure which developed subsequently was interpreted as being caused in part at least by the maintenance of the observed increase in blood and interstitial fluid volumes. Hemodilution of sufficient degree to reduce the serum protein as much as 10 to 15 per cent was shown to occur with inactivity and assumption of the recumbent posture (110). The resultant increase in plasma volume under such conditions was correlated with nocturnal attacks of paroxysmal dyspnea in cardiac patients.

Water Intoxication and Adrenal Cortical Function

Interest in the pathological physiology of excessive water ingestion has been revived by recent studies on the role of the adrenal cortex in water metabolism. Adrenalectomized mice, dogs, and rats show a markedly reduced diuretic response to administration of water in excessive amounts and a greatly increased susceptibility to water intoxication with generalized weakness and convulsions (111, 112, 113). Desoxycorticosterone acetate (114) and even more strikingly both adrenal cortical extract and 17-hydroxy-11-dehydrocorticosterone (115) were found to exert a protective effect against water intoxication in normal animals and to abolish the increased susceptibility of adrenalectomized animals. A concen-

trated cortin-like extract from normal urine was found to have a similar effect in adrenalectomized rats (116). Contrary to what might be expected, unless the operated animals had previously been depleted, adrenalectomized animals were found to lose much less chloride externally than did normal animals when both were subjected to the same degree of forced water intake (117). The reduction in plasma chloride under the same conditions was greater in the adrenalectomized animals. While the plasma protein level fell as much as 25 per cent in adrenalectomized rats, the hematocrit reading was unchanged or increased as a result of water intoxication. This latter effect, which was found to be due to swelling of the red blood cells, was more marked in adrenalectomized than in normal animals. The volume of the extracellular fluid was found to be reduced in severe water intoxication, the large amount of water retained having entered the cells of the body. Water intoxication produced no increase in blood pressure or in the degree of hypoglycemia in adrenalectomized rats. That the impaired diuretic response to water is not dependent upon the antidiuretic function of the neurohypophysis has been demonstrated (118). Oxygen consumption was reduced 40 per cent below normal in water intoxication. This might be explained in part at least on the basis of chloride loss (119). Plasma protein was said to be lost into the tissues in large amounts in adrenalectomized animals subjected to water intoxication. This is assumed to be a result of capillary leakage, but evidence for the latter is not convincing. Although there is no reason to believe that adrenal function is disturbed in idiopathic epilepsy, the convulsive response to forced water drinking and pitressin administration, and the protective effect of desoxycorticosterone acetate in this condition have been shown to resemble the reactions of the adrenalectomized animal very closely (120). Normal rats made hyperthyroid by administration of 0.2 mg. of thyroxine daily for three to six weeks showed an increased diuretic response to water and a marked resistance to water intoxication, as compared to normal rats (121). The latter did not appear to be due to increased diuresis alone, but presumably in part also to the well known hypertrophy of the adrenal cortex which has long been known to develop in hyperthyroidism. An observed smaller loss of chloride by way of the kidneys and a less marked fall in plasma chlorides in the hyperthyroid, as compared with normal rats, tend to confirm this interpretation. Furthermore,

adrenalectomy abolished the characteristic effects of hyperthyroidism.

Body Fluid Changes in Shock and Allied Conditions

The exigencies of war have caused a large number of investigators to turn their attention to the problems of shock, a condition which involves profound disturbances in the composition and distribution of body fluids. This pathological state is produced in man most frequently by extensive burns, crushing wounds, or severe hemorrhage, or by a combination of any two or more of these injuries. For experimental purposes, shock has been produced most frequently by occluding the circulation of the entire lower limb of an animal for a period of five hours (shock developing after release of the tourniquet), by blunt trauma to the extremity (under anesthesia), or by bleeding the animal to a point of marked arterial hypotension or until respiration has shown signs of failing. The combined investigations of a large number of workers have resulted in the general agreement that traumatic shock, no matter what the cause, is characterized by (*a*) marked diminution of the cardiac output, (*b*) reduction in the velocity of blood flow through the peripheral vascular bed, (*c*) reduction of the volume of venous return to the heart, (*d*) eventual fall in arterial blood pressure, (*e*) diminution in urine excretion, (*f*) increase in acid metabolites in the blood, and (*g*) decrease in the plasma carbon dioxide capacity. As the circulating plasma volume and velocity flow decrease, severe asphyxia of the peripheral tissues develops. The changes in the renal vascular dynamics resulting from peripheral circulatory failure have been shown by clearance studies to account for the marked oliguria or anuria of shock, an effect due to reduced glomerular filtration instead of increased tubular reabsorption (122). Blood appears to be shunted away from the kidneys during shock. Local loss of fluid from the blood stream into the area of injury has been shown to account very largely for changes in the fluid content of the vascular system. This has been amply demonstrated (*a*) by preventing the development of shock by application of a tourniquet or pressure cuff or a tight cast or bandage to the injured limb (123, 124, 125), (*b*) by direct measurement of the amount of fluid lost to the affected part (e.g., an extremity) and comparing it with the fluid lost from the blood, and (*c*) by use of dyes, radioactive elements, and tagged proteins as tracer substances. Plasma pro-

teins tagged with isotopes of sulfur, bromide, and iodide (S^{35}, Br^{82}, I^{131}) have been used to test the capillary leakage hypothesis in hemorrhagic, tourniquet, and burn shock (126, 127). No evidence of leakage in the uninjured general capillary bed was found at any stage of shock. There was, however, extensive capillary leakage of the tagged proteins in the areas of injury. Study of tagged red blood cells showed one-fifth of the capillary blood to become stagnated or trapped out of the active circulation as shock deepened. The progressive decline in shock appeared to be due not to a fall in total plasma volume, but to progressive reduction in the volume of actively circulating plasma. In experimental shock produced by blunt muscle trauma and occlusion of the circulation to a hind limb for a few hours, fluid lost to the injured extremity has been found to exceed the measured decrease in plasma volume, which finding indicates that general capillary damage and fluid and protein loss does not occur in the phase of development of shock, but instead that fluid is added to the plasma as a compensatory phenomenon (128). This latter change was found to produce hemodilution, but the fluid entering the blood stream from the uninjured parts of the body was found to be poor in protein. In an extensive clinical study (129, 130), hemodilution was found most commonly in those patients with shock due to skeletal trauma or hemorrhage, while hemoconcentration was found most commonly in those in shock from extensive burns or abdominal wounds. Other experimental evidence has been presented also to demonstrate that the increase in capillary permeability observed in traumatic shock is confined to the area of injury (131, 132). The lymph has been shown to contain no capillary permeability factor in traumatic shock (133). Fatal shock due to blunt trauma of leg muscles under ether anesthesia has been found to be accompanied by a small but significant rise in plasma potassium a considerable time before death and a one hundred to two hundred per cent rise just prior to death (134). Fluid loss from the circulation was regarded by the authors of this report as the major cause of death, although the high plasma potassium was considered to be a possible contributing factor. As might be expected, the severity of shock produced by applying a tourniquet and traumatizing an extremity, and the related disturbance in fluid balance have both been found to be much greater when the tourniquet is applied continuously than when it is released for two out of every thirty

minutes of a five-hour experiment (135). When shock was produced by graded hemorrhages in eleven nondehydrated and fifteen dehydrated unanesthetized normal dogs, hemoconcentration was found to occur in 18 per cent of the former and in 53 per cent of the latter (136). Volume studies showed additional plasma loss after development of shock. Hemodilution occurred in the nondehydrated dogs, which probably accounts for the fact that they tolerated a greater percentage of blood loss than did the dehydrated animals. In fatal shock produced in dogs by repeated hemorrhages (10 cc. per kg. of body weight) it was found (137) that the compensatory mechanisms following such blood losses require time and that the beneficial effect of time is progressive and directly proportional to the interval between hemorrhages. Any intervals larger than two hours were found to be significant, and an interval of twenty-four hours permitted a total blood loss equivalent to twice the normal blood volume without fatality. With hemodilution resulting from the inflow of tissue fluids there was some addition of albumin but not globulin. Replacement of the blood lost by physiological saline solution did not prolong life and appeared to interfere with natural compensation. In dogs, susceptibility to hemorrhagic shock has been found to be increased as much as 67 per cent if the animals have previously been made hypoproteinemic by means of plasmapheresis (138). The effects on fluid shifts within the body of withdrawing slightly more than a pint of blood from a normal adult subject and of transfusing a slightly smaller volume of red blood cells into anemic patients have been found to vary considerably from person to person without obvious explanation (139). Fluid from the tissues enters the blood in both conditions, however, and the plasma protein falls. Some of the entering fluid remains in the plasma and some enters the red blood cells, as indicated by an increase in mean corpuscular volume and total red cell volume. These changes suggest that the entering fluid has a lower osmotic pressure than plasma. In these studies, changes in hemoglobin were found to serve as a reliable indication of fluid shifts only when the plasma volume was also known.

In contrast to the extreme changes in volume and distribution of the body fluids observed in traumatic shock, those in so-called orthostatic or gravity shock produced by suspending four-legged animals in a vertical position, have been found to be slight. Rabbits so placed for some hours showed changes in some of the blood

constituents due to peripheral circulatory deficiency and anoxia but no constant or significant alterations in the hematocrit reading, plasma specific gravity, protein, calcium, or sodium, or in the red blood cell count (140). Although the urine flow was suppressed, hemoconcentration did not occur. In the dog under barbiturate anesthesia, vertical suspension with the feet down to the point of gravity shock produced a fall in the plasma proteins and an increase in the protein concentration of the lymph (141). These conditions were all reversed within thirty minutes, however, after the animal was returned to the horizontal position. Dogs maintained in this abnormal position were found to be extremely sensitive to withdrawal of comparatively small volumes of blood, irreversible failure following. This could usually be prevented and the response to tilting improved by the infusion of saline solution or blood during the upright period.

Blood Substitutes and the Treatment of Shock

Because of the obvious difficulty of obtaining fresh, compatible, whole blood promptly enough for transfusion purposes under many circumstances, extensive investigations have been carried out in search of suitable blood substitutes. In one study (142), the efficacy of various fluids was determined as judged by their reduction of the mortality from a standard massive hemorrhage which caused death in 84 per cent of fifty control dogs. Heparinized dog plasma, which proved to be the best, reduced the mortality to 6 per cent. Pooled serum reduced it to 26 per cent, the best of a series of gelatin saline solutions (5 per cent gelatin) to 40 per cent, and physiological saline solution alone to 58 per cent. Citrated blood or plasma in the volume required was found to be lethal due to the large amount of citrate injected. Pectin and gum acacia solutions and some preparations of gelatin were found to be undesirable because they produced pseudo-agglutination of the red blood cells. A gelatin solution having little or none of this latter undesirable effect, however, would appear from these studies to be second only to plasma as a blood substitute. In shock produced in unanesthetized dogs by repeated bleedings of 10 cc. per kg. of body weight, the survival time (3.6 hours in controls) was increased to 6 hours by heparinized plasma, 4.5 hours by citrated plasma or serum, 5.15 hours by hydrolyzed protein (amigen 5 per cent), 4.2 hours with a 5 per cent solution of pure amino acids in saline, but not at all by

glucose or saline solution alone (143). Plasma proved to be superior to a 6 per cent solution of gelatin in saline during the second phase of burn shock, but the latter was very satisfactory and definitely superior to saline for temporary use in both burns and hemorrhagic shock (144). Pseudo-agglutination of red cells occurred and the sedimentation rate was increased by gelatin, but these effects were found to be transient and appeared to do no harm. In the type of shock produced by release of a tight tourniquet after occlusion of the circulation to a hind limb for five hours, it was found that plasma given in a single dose of 25 cc. per kg. of weight at the time of release did not prevent shock and death, whereas the same amount given in five divided doses saved every dog so treated (145). Shock produced in anesthetized dogs by subjecting one hind limb to 750 pounds of pressure for seven hours was fatal in twenty-five of twenty-six untreated animals and in ten of eleven given a single massive intravenous infusion (40 cc. per kg. of body weight) of 5 per cent gelatin in saline solution at the time of removing the pressure (146). On the other hand, when the same amount of gelatin solution was administered in six divided doses over a period of eight hours, following removal of the pressure, shock was prevented in nineteen, or 73 per cent of twenty-six dogs. Heparinized plasma gave no better results. Intermittent infusions of saline alone resulted in survival of 35 per cent. Similar or slightly better results were obtained in shock due to blunt trauma and tourniquet release (147). Saline solution was highly beneficial if administered before shock set in, but was without effect after it had developed. Some of the same authors (148) compared the values of different infusions in experimental shock produced in anesthetized dogs by a shotgun wound of one hind leg. Whereas a single massive infusion of plasma given at once prevented shock in but two of fourteen animals, the same volume of plasma given in five divided doses over seven hours prevented shock in eleven of fifteen animals. Gelatin and saline solutions given intermittently prevented shock in two-thirds and one-half of the traumatized dogs respectively. Saline solution if given early has been shown to be of definite value in types of shock not involving plasma protein loss. Since saline solution was found to be quite superior to isotonic glucose solution, it was concluded by one group of workers (149) that its effect is not due merely to the simple addition of fluid.

A study of the fate and effects of gelatin given intravenously

to normal dogs in a concentration of 6 per cent in saline solution and in a volume equivalent to 1 per cent of the body weight showed 55 to 71 per cent of that injected to have disappeared from the plasma within six hours and 81 to 87 per cent in twenty-four hours. From 20 to 29 per cent appeared in the urine on the first day. A marked and almost immediate decrease in the total circulating red cell volume persisted for at least three days (150). Such gelatin solutions were found to exert a fairly strong diurectic effect (151). Under conditions of tourniquet shock in which the plasma volume was markedly reduced, a 4 per cent gelatin in saline solution given in a volume equivalent to 2.5 per cent of the body weight caused a considerable increase in the circulating red cell volume six hours after the injection, as compared with the control volume (152). The rate of disappearance of gelatin from the blood plasma was no greater than in normal animals. This observed tendency to preservation of blood volume complements the observations made in reverse order in the presence of anemia by other workers (153). A buffered pectin solution (1.5 per cent, exerting an oncotic pressure of 67 cm. of water) was found to be useful as a blood substitute in hemorrhagic hypotension during the first thirty-minute period only (154). No correlation was found between maintenance of hemodilution and favorable hemodynamic reactions. In the opinion of the authors, the demonstrated ability of a colloid (*a*) to maintain an effective oncotic pressure over a considerable period of time, and (*b*) to increase blood volume of normal animals does not appear to be a satisfactory criterion of its physiological usefulness. Pectin solution proved to be no better than saline solution in maintaining animals subjected to hemorrhagic hypotension (155).

Following shock in which blood is lost some time is required to completely restore the plasma volume if proteins are not added, because fluid entering from the tissues contains but little. Since there appears to be no significant reserves of red cells, whole blood transfusions have been found to be desirable after the emergency fluids have been given (156). Concentrated human serum albumin solution was found by recent clinical experiments (157) to hold fluid in the blood stream approximately comparable to its osmotic activity, one gram of retained albumin increasing the plasma volume by 23 cc. This extra fluid was drawn from the tissues or retained from crystalloid solutions administered. Except for the lack

of red cells for restoration of oxygen transport to the tissues, this albumin solution is comparable with blood. The average increases in plasma volume per gram of retained albumin reported by others working with the concentrated human albumin solutions have ranged between 16 and 17.4 cc. (158, 159, 160). By *in vitro* measurements of osmotic pressure, the water-holding value has been estimated to be 18 cc. per gram of albumin (160). Serum protein injected intravenously in normal animals has been found to leave the blood stream at a constant rate similar to that of a colloidal dye used in determining plasma volume (161). Such infusions result temporarily in loss of water from the red cells and in a degree of diuresis roughly proportional to the increase in plasma volume. The fate of injected plasma protein under various conditions has been determined in dogs with a high degree of accuracy (162). It is evidently added to a common reserve or protein pool and is then utilizable, not only for replacement of lost serum proteins, but for fabrication of new hemoglobin molecules and body cell proteins as well, in accordance with the special needs of the organism. In the type of shock showing diminished plasma volume, such protein stores furnish serum albumin to the blood and more of any injected protein is probably retained as unchanged plasma protein.

While long known to be an accompaniment of severe shock, acidosis has received little direct attention by either physiologists or clinicians. However, in a recent study (163) on the effects of administering sodium bicarbonate in addition to blood and glucose to dogs subjected to fatal hemorrhagic shock, it was found that only 25 per cent survived when whole blood alone was given to replace that lost after the arterial blood pressure had been reduced to 50 mm. of mercury or less. When the blood was supplemented by sodium bicarbonate and glucose solution, 62.5 per cent survived. Adrenal cortical extract and desoxycorticosterone acetate both had the effect of reducing the amount of fluid lost into the edematous limb in shock produced by venous occlusion of an extremity (164). From the viewpoint of water metabolism and circulatory response, application of heat has been shown to be contraindicated in shock (165).

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PHYSIOLOGICAL EFFECTS OF HEAT AND COLD

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Due to the war the interest of many physiologists in the field of physiological temperature regulation has been directed to unexplored borderline regions between pathology and physiology. These investigations have been concerned with the physiological responses to heat or cold of such a degree that ordinary physiological mechanisms break down and pathological changes are seen. Stimulation for investigation of the human response and limitations to excessive cold has arisen from two sources. One source is the need for data on the physiological changes resulting from prolonged exposure such as occurs in lifeboats in northern oceans, men fighting in semiarctic terrain, and aviators who have made forced landings in the snow. The other stimulus is the need for data on cold therapy. While the hypothermia of cold therapy is of doubtful therapeutic value the possibility of usefulness still exists and stimulates research on maintained low body temperatures. The physiological and pathological effects of cold are reviewed by Lewis (1, 2, 3) in a series of papers which could be considered as classics on the subject were it not for the fact that the review is confined almost exclusively to the work of Lewis and his colleagues. The physiological problems involved in excessive and prolonged cold are reviewed in an excellent article by Ungley & Blackwood (4). In investigations on the effect of desert conditions the work of Keys (5 to 8) and colleagues is particularly outstanding. Mills and colleagues (9, 10, 11) have shown that the dietary requirements for a temperate environment are not adequate for an environment of excessive heat. Edwards & Irving (12, 13) have two interesting papers on comparative temperature regulation concerning the seasonal activities of marine invertebrates, one of which is completely poikilothermic and the other has activities suggestive of a certain degree of homeothermy. There are two papers, one by Tompkins (14) and the other by Klaften (15), concerning the fluctuations in rectal or uterine temperatures as related to the menstrual cycle and hormone effects which might have some bearing

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on the problem of civilized man in his reproductive years of trying either to avoid or bring on conception. There are several good papers on frostbite and physiological reactions to cold environments. There are many other outstanding papers in the field of temperature regulation which will be mentioned in detail in the following pages. In general, the contributions to this subject in the published journals have been fewer than in past years. A number of papers have been unobtainable by the author. Foreign articles are practically nonexistent. A large amount of useful physiological information is contained in the confidential files of the Armed Forces and it is hoped that an effort will be made in the future to publish those articles which relate to useful physiology without divulging classified military information.

During the past year the investigators on physiological temperature regulation received with regret the news of the death of Prof. H. G. Barbour. His work on temperature regulation, water metabolism, pyretic, and antipyretic drugs was internationally known. His enthusiasm and stimulating personality were always in evidence at his laboratory at Yale University and at the Physiological Society meetings. His contributions to physiology dating from his "Wärmestich" experiment of 1912 to his last paper, that of Barbour, McKay & Griffith (16) in 1944, were made in an era of rapidly expanding knowledge of physiological temperature regulation.

The Nervous Control of Temperature Regulation

Nervous control of shivering.—For many years physiologists have accepted without question the results of Sherrington and others that shivering is dependent on motor impulses from the central nervous system. McDowall (17) using the skinned limb of a chloralosed cat has observed shivering movements with nervous connections from the central nervous system severed. No details of the experimental procedure are given in the brief summary.

Central cold narcosis.—De Almeida (18) used a nerve-muscle preparation from a frog, *Rana pipiens*, with a portion of the lower part of the spinal cord attached to the nerve. Thermal reflex block in spinal centers was produced by warming or cooling the isolated spinal cord. Heat paralysis occurred with spinal cord temperatures above 29 degrees C. and cold paralysis occurred with temperatures below 14 degrees C. The effect was reversible with conduction

being restored when the spinal cord temperature was returned to the region of 14 to 29 degrees C. The temperatures from which recovery was possible do not include the temperatures causing permanent tissue damage.

Sympathetic nervous control of sweating.—Richter & Whalen (19) using lightly anesthetized cats exposed and stimulated the sympathetic ganglia at the fifth lumbar level. Zinc-zinc sulphate electrodes on the paws were used to "pick up" action potentials. A single shock applied as a stimulus elicited a monophasic action potential from the paw while induced currents of 136 to 375 shocks per minute caused "complete tetanization of the sweat glands" as revealed by action potentials from the paw.

Brain tumor and body temperature.—Brodsky, Cohen & Gray (20) have added another to the growing list of cases in which an early symptom of brain tumor was an elevated mouth temperature. At subsequent operation a meningioma was removed from above the sphenoid ridge. Apparently pressure in this region was transmitted to the hypothalamus causing a condition resembling the fever observed in the early "brain puncture" experiments on animals.

Comfort and skin temperature.—The sensation of comfort as related to peripheral thermal end organs and rectal temperature has never been clearly established. Burch & Sodeman (21) in an environment of 105 degrees F. and 75 per cent humidity which ordinarily would cause discomfort were able to produce a comfortable sensation by cooling a small region of the skin by immersing an arm in water. Occluding the circulation of the immersed arm causes the discomfort to reappear.

Nervous activity and blood lactate.—Swan (22) measured the blood lactate levels of dogs during the course of a year and found that the blood lactate was a maximum when daily temperature fluctuations were a maximum. He attributed the increased blood lactate at this time to influences of a "nervous nature" associated with physiological temperature regulation.

Endocrine Control of Physiological Temperature Regulation

Adrenal medulla.—The endocrine glands which function in the control of body temperature are primarily the adrenal medulla and thyroid and secondarily the gonads. The calorigenic action of

epinephrine in the rat, where chemical temperature regulation is more effective than in dogs and man, has been measured by Bunnell & Griffith (23). An injected dose of 0.02 grams epinephrine per 100 grams body weight caused a rise in oxygen consumption rate which reached a peak of 30 to 35 per cent above normal in one-half to one hour and subsided to the basal control value in four hours. The response in young rats was greater and subsided faster than the response for old rats.

Thyroid.—Leblond, Gross, Peacock & Evans (24) used as a measure of thyroid activity the rate at which injected radioactive iodide (as sodium iodide) was taken up by the thyroid gland of rats. An exposure to cold in an environment of 1 to 2 degrees C., lasting seven to twenty-six days, resulted in an uptake of radioactive iodide two to three times that of control rats kept at room temperature. On the other hand a longer exposure to cold of forty days reduced thyroid activity to a value less than that of the controls. Thus, short exposure to cold stimulates thyroid activity but prolonged exposure results in a reduction of activity. This method is promising as a measurement of gland activity and careful correlation of simultaneous histological, metabolic, and radioactive iodide methods of measuring activity would be useful.

Circulation

Taylor, Henschel & Keys (6) state that acclimatization to hot environments consists of a conditioning of the cardiovascular system. Conditioning is estimated by measuring pulse rates and rectal temperatures when a definite working rate is maintained in a hot environment. As conditioning proceeds the pulse rate and body temperature decrease to a level which indicates the conditioned state.

Landsteiner & Hayes (25) have perfused rabbit and cat hearts and have varied the temperature of the perfusing fluid between 22 and 50 degrees C. With perfusion fluid at 22 degrees C. bradycardia was observed. The heart rate of the rabbit was reduced 60 to 80 beats per minute and that of the cat 40 to 50 beats per minute below the normal rate. With perfusion fluid at 50 degrees C. tachycardia occurred with the heart of the rabbit beating at a rate of 40 to 60 and that of the cat 20 to 40 beats per minute above normal.

Spealman (26) measured the difference between skin temperature, Ts, and water temperature, Tw, when the human hand was

immersed in water at a series of temperatures from 5 to 25 degrees C., at a room temperature of 16 degrees C. He found that Ts-Tw was a minimum at water temperatures between 15 to 20 degrees C. Comparative changes of blood flow, estimated from the expression Ts-Tw/37-Tw, were made and it was found that blood flow through the hand was a minimum at 20 degrees C. water temperature and increased as the temperature of the water rose above or fell below this value. Barcroft & Edholm (27) measured blood flow in the human forearm by the Lewis & Grant plethysmographic method with the arm immersed in water the temperature of which varied in a series of experiments from 13 degrees C. to 45 degrees C. These investigators found the blood flow progressively increased from 0.5 to 4.0 mls. per 100 mls. forearm per minute as the water temperature was raised from 13 to 35 degrees C. and the blood flow remained at approximately the same level throughout a two hour experiment. At temperatures 38 to 42.5 degrees C. during the course of a two hour experiment the blood flow at first increased and then decreased, while at 45 degrees C. the blood flow increased to a maximum value of 18 to 20 mls. per 100 mls. forearm per minute.

The thermal vasomotor reflex of individuals with thiamine and riboflavin deficiency was measured by Roth, Williams & Sheard (29). In contrast with the results of earlier workers the Mayo Foundation group found no significant changes in the thermal vasomotor reflex with this type of vitamin deficiency.

Aschoff (28) has studied the effect of cold on isolated perfused arteries. He found that when measures are taken to compensate for viscosity increases with cold a denervated artery will actually dilate slightly as the temperature is decreased downward from body temperature.

Physiological Response to Warm Environments

Sweating.—The large loss of vitamins, especially vitamin C, which was once thought to occur by sweating has been shown in recent studies to be incorrect. Kirch, Cornbleet & Bergeim (30) have shown that if a nonspecific reduction method for estimation of vitamin C is used a high value of reducing substances is found in sweat. If a specific vitamin-C oxidase is used to destroy vitamin C and the reducing values again determined the reducing value is high. This indicates that the nonspecific reducing substance in

sweat is not vitamin C. This difficulty resembles the earlier controversies concerning blood sugar in which reducing substances other than sugar were being designated as sugar. With the newer and more reliable methods of analysis vitamin loss in the sweat appears to be negligible. Mickelsen & Keys (5) estimate that the maximum loss of vitamins with sweating of ten liters per day would be less than 10 mgs. of ascorbic acid and 50 micrograms of thiamine.

Richter & Whalen (19) induced the psychogalvanic response in a cat's paw by stimulating the sympathetic chain in the lumbar region. Single shocks produced a response lasting five seconds after a latent period of 0.6 seconds. Tetanization of the sweat glands (indicated by the galvanic response) resulted with shocks of 136 to 375 per minute.

Neumann *et al.* (31) measured sweating from a cat's paw by the condensation of evaporated sweat in a dry ice condenser. Under basal conditions with no sweating the rate of evaporation of water was 7 to 10 mgs. per 30 square centimeters of cat's paw per 15 minutes. After exposing the cat to radiant heat and producing an elevation of rectal temperature to 40 to 41 degrees C. the rate of sweating became four to six times basal. The sciatic and saphenous nerves were cut and sutured or crushed. This procedure eliminated sweating which slowly returned after fifteen to thirty weeks following sectioning and suturing and fifteen weeks after crushing.

Hemingway (32) measured rate of sweating from human subjects who were motion sick and who sweated profusely in a cold environment with a falling skin and mouth temperature. Insensible perspiration without sweating was 0.08 to 0.13 mgs. per sq. cm. per minute. During "cold" sweating the rate increased to 0.30 to 2.2 mgs. per sq. cm. per min.

Wolkin, Goodman & Kelley (33) from observations on men who were overcome by heat on the desert describe a clinical syndrome which they consider differs from typical heat exhaustion and heat stroke. In the new type of heat susceptibility there is profuse sweating of the head and neck but not from skin below the neck. Before the onset and after recovery sweating from areas below the neck was normal. In other respects the condition has symptoms of both heat exhaustion and heat stroke.

Dietary requirements.—Taylor *et al.* (8) have determined the sodium chloride requirements and the serum chloride of men work-

ing to exhaustion in a hot environment (120 degrees F., wet bulb 85 degrees F.) who were sweating to the extent of 5 to 8 liters of sweat per day. These investigators conclude that under the most severe conditions of tropical fatigue the sodium chloride requirement is 13 to 17 gms. per day and no advantage is to be gained by exceeding this quantity in the diet. Eight of their men had serum chloride concentrations less than 100 m.eq. of chloride per liter with the lowest 80 m.eq. per liter and the average 94.6 m.eq. per liter. None of these men had heat cramps but five of the eight had heat exhaustion. This finding is of particular interest since in cases of muscle cramps in men working in hot environments it has been generally believed that sodium chloride loss has been the chief factor. As a result of the experiments of Taylor *et al.* it may be necessary to look for factors other than sodium chloride deficiency in the etiology of muscle cramps occurring in industry.

Cohn & Soskin (34) were able to reduce oxygen consumption rate of dogs (anesthetized with pentobarbital) as much as 20 to 40 per cent below basal values by depriving the animals of sodium chloride. When animals deprived of sodium chloride were given sodium phosphate in an amount sufficient to replace the sodium the oxygen consumption rate increased only 6 to 10 per cent. Replacement of chloride increased the oxygen consumption rate 15 to 30 per cent. The chloride depleted animals exhibited an increase in blood lactic acid to a value of 31 to 106 mgs. per 100 mls. of blood.

Sarett & Perlzweig (35) investigated the effect of high and low intake of the B vitamins on the gain in weight of growing rats. The rats were divided into four groups with two groups kept at 75 degrees F. for 22 to 25 days and two similar groups at 90 degrees F. Of the two groups kept at each temperature one group received minimal adequate vitamins of the B complex (thiamine, pantothenic acid, riboflavin, and nicotinic acid) and the other group received excess amounts of the vitamins. The food intake of the rats at 75 degrees was regulated to equal that of the animals in the warmer environment. The high vitamin diet caused a greater gain in weight at both temperatures than the minimal adequate diet. The greatest weight gains were observed on the high vitamin diet at 91 degrees F. The rats in this group had relatively more fat and less water in the carcasses than rats in the other groups. Mills, Cottingham & Mills (11) found that rats on a vitamin-K deficient diet had four times as much internal hemorrhage when kept at

90 to 91 degrees F. as rats kept at 68 degrees F. Mills estimates that the dietary requirement of vitamin K per kg. of diet for rats maintained in a warm environment is double the requirement of a diet for a normal (68 degrees F.) environment. Mills (9) found that the dietary requirement of pyridoxin and riboflavin was the same in a warm as in a cool environment. Of all the B vitamins thiamine and choline are the only ones which must be increased for normal growth in a warm environment.

Mills (10) found that rats raised in an environment at 68 degrees F. eat more food and are less likely to show retarded growth on a low protein diet (6 to 18 per cent casein) than rats raised at 91 degrees F. There is little difference in growth rates in the two environments when a high protein diet (24 to 36 per cent casein) is fed. Cystine, added to supplement the deficiency of casein, is more effective at 91 degrees F. than at 68 degrees F.

From the papers just cited an interesting result is noted concerning dietary requirements. Ingested food is either burned or stored. In a cool environment a rat which depends more than other animals (such as the dog, or human) on chemical temperature regulation (combustion of food stuffs) to maintain body temperature will use relatively more of the ingested food for combustion and less will be stored. At a higher environmental temperature, e.g., 90 degrees F., with the same food intake more will be stored and less will undergo combustion in the tissues. For a given increment of weight in a growing rat less food will be required in a warm than in a cool environment.

Acclimatization to desert environments.—Acclimatization to desert environments has been measured by two groups of investigators, Robinson, Turrell, Belding & Horvath (36) of Harvard University and Taylor, Henschel & Keys (6) at the University of Minnesota. Similar methods for evaluating acclimatization were used by each group, the methods consisting of measuring pulse rates and rectal temperatures after working at a predetermined rate in the desert environment. The Minnesota group used more subjects and had the men live in a simulated desert environment for two to eight days while in the Harvard experiments the subjects would work for several hours each day under desert conditions and live the rest of the day in a New England environment. In the unconditioned subject pulse rate and body temperature would be elevated at first and as conditioning developed the pulse rates and

body temperatures dropped to a constant value. When this constant value was reached acclimatization had occurred. Acclimatization as estimated by these criteria required four to five days according to the Minnesota group and according to the Harvard group 80 per cent of acclimatization occurs during the first seven days with the remaining adaptation being developed within twenty-three days.

Keys and colleagues state that acclimatization consists of an adjustment of the cardiovascular system to the strenuous overwork required for cooling. The rate of sweating was found to remain unchanged whether or not acclimatization had occurred.

Body Temperatures and Their Variations

Ovulation and body temperatures.—Tompkins (14) has measured the rectal temperature of women under "basal" conditions before rising in the morning. He found that the "basal" rectal temperature during the menstrual cycle is relatively low during the first part of the menstrual month and drops to a minimum at the time of ovulation. Thereafter during the post ovulation period of the cycle the temperature rises progressively. Ovulation can be detected by a low temperature followed by a sharp rise and Tompkins recommends sexual intercourse at this time for most probable fertilization of the ovum. Klaften (15) measured body temperatures of women at several places including mouth, rectum, vagina, and cervix and body of the uterus. The most significant temperature changes, related to the events of the menstrual cycle, were the temperature changes of the body of the uterus and Klaften (15) has described a special thermometer for this purpose. Klaften found that the uterine temperature was a minimum on the fifth day following the beginning of menstruation. A rise in temperature followed until the twelfth day corresponding to ovulation. This was followed by a drop in temperature with a premenstrual rise on the twenty-fifth to twenty-seventh day. The average uterine temperature fluctuation varied from a minimum of 37.3 degrees C. (postmenstrual) to a maximum of 38.1 degrees C. (ovulation peak and premenstrual).

Shock and brain tumor.—A symptom of shock which is frequently mentioned in first aid manuals is the cold "clammy" skin. Wright & Devine (37) measured rectal, mouth, and wrist skin temperatures of patients in shock and normal subjects in a similar

environment. They found the average temperatures as shown in the following table.

Condition	Number of subjects	Rectal temp.	Mouth temp.
Normal	9	98.6	97.5
Shock	19	99.3	96.7

They state that the skin temperature of the patients was no criterion of shock and they recommend caution in warming or covering a patient in shock unless his body temperature is known. It might be pointed out that in shock cold sweating occurs which could account for the "clammy" feeling of the skin without a significant change in skin temperature.

Brodsky, Cohen & Gray (20) have reported a case of a brain tumor in the frontal region above the sphenoid ridge in which an early symptom was an elevated temperature without evidence of infectious origin. From a number of such cases in the literature evidence is accumulating that this is a useful diagnostic sign for brain tumor in the vicinity of the hypothalamus.

Lethal temperatures of fowls.—Randall (38) has measured the upper and lower viable limits of cloacal temperature of the fowl. He found that the first indication of physiological breakdown by overheating was a reduction in respiratory rate which occurred at 45.5 degrees C. At 47 degrees C. the heart rate commenced to decrease. The lethal temperature in hyperthermia was estimated to be within the cloacal temperature range of 46.0 to 47.8 degrees C.

Muscle temperature.—Barcroft & Edholm (27) measured the temperature in the brachioradialis muscle near the middle of the thick part of the forearm and one inch from the surface during a series of two hour experiments in which the forearm was immersed in water. Ten experiments were performed with water temperature values ranging from 12 to 45 degrees C. The equilibrium muscle temperature ranged from 18 to 44 degrees C.

Pyretic protein in exudates.—Menkin (39) has isolated a protein of the euglobulin fraction from exudates which will cause fever when injected into dogs. This pyretic action cannot be induced by pseudoglobulin fractions from canine exudates, the albumin fraction of canine exudates, or the euglobulin fraction of normal serum.

Age and Temperature Regulation

Development of homeothermy.—Randall (38) found that the cloacal temperature of newly hatched chicks was 38 degrees C.

During the first ten days after hatching the cloacal temperature increased to the normal adult value of 41 degrees C. Shivering occurs one week after hatching.

Calorigenic action of epinephrine and age.—Bunnell & Griffith (23) measured the oxygen consumption rate of rats before and after an injection of epinephrine of dosage 0.02 mg. per 100 gms. rat. For young rats of two to six months of age the usual increase of oxygen consumption rate occurred reaching a peak of plus 40 per cent after one hour and decreasing to the basal level after two and one half hours. Older rats of nineteen to twenty-four months of age had a calorigenic response curve which was flatter with a maximum value of plus 20 per cent in oxygen consumption rate and with a duration of the same value as that of younger animals.

Age and oxygen consumption rate.—Will & McCay (40) measured the oxygen consumption rate of rats fed a low calorie diet which retarded growth for 800 to 900 days. The results are shown in the following table.

Condition	Number of animals	Cals. per sq. m. per hour	Cals. per kg. per hour
Low calorie diet	11	29.6 ±0.67	4.50 ±0.10
Normal controls	9	32.4 ±0.69	3.41 ±0.09

In terms of surface area the rats with retarded growth had a lower oxygen consumption rate but in terms of calories per kg. the rate was higher for the retarded growth animals when compared with controls. When rats were fed a growth-retarding diet for 900 days followed by a normal diet, the "realimented" rats had a lower oxygen consumption rate in terms of cals. per kg., but a rate statistically insignificant in terms of cals. per sq.m. The interesting finding in the observations is the small variation from control values caused by low calorie diets.

Comparative Physiological Temperature Regulation

With our present knowledge of physiological temperature regulation it is generally believed that all animals lower in the phylogenetic scale than mammals and birds are devoid of physiological means for regulating their body temperature. A recent investigation by Edwards & Irving (13) has revealed that an invertebrate, the sand crab *Emerita talpoida* Say, has a rudimentary form of chemical temperature regulation. The sand crab, in contrast with other shore animals, remains active during the winter

in northern latitudes. Edwards & Irving found a seasonal variation in the oxygen consumption rate of the sand crab when measured at a temperature of 3 degrees F. The oxygen consumption rate of sand crabs collected during the winter was four times the rate of animals collected during the summer. On the other hand, the beach flea, *Talorchestia megalophthalmia* (12), which in the winter burrows four feet into the beach sand and becomes inactive, has no variation of oxygen consumption rate with seasonal environmental changes of temperature. The beach flea is a true poikilotherm.

Hypothermia

Refrigeration anesthesia.—Mock & Mock (41) and O'Neil (42) have used cold as a means of anesthesia particularly for operations on extremities which are convenient for local cooling. Cold in the form of ice packs is used and reduction in blood flow to the cooled extremity is produced by means of a tourniquet. According to Mock & Mock (41) the tissue temperature falls to a value of 0.5 to 5.0 degrees F. above freezing. Anesthesia is sufficient to allow crushing of the sciatic nerve without pain. In trauma where it is desirable to delay an operation until a shock condition subsides the injured member can be cooled until ready for operation. The cooling reduces the blood flow through the injured region and reduces the severity of shock. O'Neil (42) recommends this method of anesthesia for patients who are "aged, undernourished, neglected and discouraged." For this type of patient who is a poor risk the mortality due to ordinary anesthetics is high and cold anesthesia is useful. For patients who are in good physical condition, cold as a method of anesthesia has little advantage over other methods. In the technique of administering anesthesia a tourniquet and ice bags are used for cooling which requires two and one-half hours. With this method of anesthesia little if any preliminary medication is required and postoperative discomforts such as nausea and vomiting are not experienced.

Drugs and recovery from hypothermia.—Barbour, McKay & Griffith (16) exposed rats to cold until their rectal temperatures had fallen to 16 degrees C. They were then removed to a room at 28 degrees C. and the recovery time determined for (*a*) body temperature to return to normal, (*b*) righting reflexes to appear, and (*c*) edema to disappear. Using these criteria for recovery the following order of effectiveness was noted for a group of drugs with

their dosages: (*a*) beta-tetrahydronaphthylamine, 5 mgs. per 100 gms.; (*b*) ephedrine, 8 to 10 mgs. per 100 gms.; (*c*) epinephrine, 1.3 mgs. per 100 gms.; tyramine, 10 mgs. per 100 gms.; (*d*) strychnine, 0.1 mg. per 1100 gms.; atropine sulphate, 10 mgs. per 100 gms.; tincture of digitalis, 0.38 cc. per 100 gms.; digifoline, 0.36 cc. per 100 gms.; and caffein, 10 mgs. per 100 gms. The drugs of group (*d*) had only slight or no effect.

Hypothermia due to anesthetics.—In agreement with previous investigators on this problem, Green *et al.* (43) found that anesthesia of dogs in an ordinary laboratory environment causes a drop in rectal temperature. Morphine, barbital, chloralosane, and sodium pentobarbital anesthesia caused a drop in the rectal temperature of dogs of 1 to 4 degrees C., which was associated with a rise in peripheral temperature of the extremities.

Minimal recoverable body temperatures.—In determining the lowest body temperatures to which an animal can be brought and from which it can recover the majority of investigators fail to mention the important item of duration time at the minimum temperature. In any question of thermal tolerance it is not only the low or high temperature but the time-temperature relation which is important. In an earlier review of the literature on hypothermia in man for treatment of cancer Talbott (44) states that the minimum rectal temperature from which a patient can recover lies within the range of 70 to 75 degrees F. If chicks one week old are cooled to low temperatures respiratory movements cease when the cloacal temperatures reach 15 degrees C., but respiration continues as the cloacal temperature is lowered to 10 degrees C. if oxygen is being breathed (38). Randall also found that the heart would continue to beat with cloacal temperatures as low as 8.5 degrees C.

Water shifts and hypothermia.—Barbour, McKay & Griffith (45) cooled rats and monkeys without anesthesia until the rectal temperature of the monkeys reached 23 degrees C. and that of the rats 16 degrees C. Serum chloride and serum specific gravity were measured. As the rectal temperature fell from the normal value during the process of cooling there was first an increase of specific gravity and serum chloride concentration, this fact indicating withdrawal of water into tissue cells in the well known hypothermic concentration reflex previously described by Barbour. When the rectal temperatures fell to values less than 30 degrees C. dilution commenced and continued as the temperatures continued to fall.

Warming caused a further dilution. Barbour and colleagues interpreted these events as first of all a reflex hemoconcentration in the cold. With rectal temperatures below 30 degrees C. the reflex mechanism failed because of cold paralysis and dilution followed.

Shivering.—When the rectal temperature is progressively reduced in a hypothermic state shivering at first increases and then decreases. Talbott (44) states that, in contrast with the earlier observations of Fay who found that shivering ceased at rectal temperatures less than 90 degrees F., he (Talbott) found intermittent shivering at rectal temperatures as low as 75 degrees F. Randall (38) found that shivering in a chick becomes less as the cloacal temperature is reduced below 30 degrees C. and ceases entirely when the temperature reaches 20 degrees C.

Tissue Injury Caused by Cold (Frostbite)

Frostbite as a military problem.—An interesting resume of frostbite as a military problem has been given by Greene (46). He has pointed out that excellent accounts of frostbite are contained in the histories of the Napoleonic and Crimean Wars as well as the War of 1914–1918. In the last war there were 84,670 cases of frostbite in the British Army. In one week ending December 16, 1916, 3,104 men received medical treatment for frostbite. In a blizzard in southeastern Europe in November, 1915, there were 15,900 cases of frostbite. Due to adequate preparation for cold in the Russian Campaign which followed the War of 1917–1918 there were only forty-eight cases of frostbite.

Course of events during frostbite.—A number of papers published during the past few years and especially since the beginning of the present war contain excellent descriptions of the course of events in frostbite and immersion foot (4, 46 to 53). In frostbite there may be actual freezing to the extent that crystals of ice form in the tissue. In immersion foot there is damage to tissue by cold without actual freezing. Injury is caused by long continued exposure to cold water, such as occurs in men adrift in lifeboats or fighting in wet and muddy terrain. Since in frostbite there is always tissue injured by cold as well as destroyed by freezing the course of events in the injured tissue of both immersion foot and frostbite is much the same. It is customary to divide these events into three stages. The first stage is that of injury and includes the period of exposure as well as first aid measures. The second stage is called the acute

hyperemic stage and occurs after the patient has been hospitalized. This period lasts for a few days and the injured extremity is warm, inflamed, edematous, and painful or anesthetic depending on the severity of the injury. The third stage is that of recovery which may last from several days to several months depending on the severity of the original injury. In this period the edema subsides, sensation returns, pain disappears, dead tissue is sloughed off, and normal function is regained.

Physiological changes in cold injury.—In the treatment of injury due to cold there are three tissues to consider, namely (*a*) the normal tissue, (*b*) the injured tissue, and (*c*) the frozen tissue. Once a tissue has been badly frozen with ice crystal formation taking place that tissue is irreparably damaged. There is, however, between normal tissue and the frozen tissue a region, which may be large in extent, consisting of injured tissue. In the treatment of cold injury it is the purpose to restore as much as possible of this injured tissue to normal usefulness. At the present time the method of therapy is controversial because there is insufficient information on the physiological changes which have occurred as a result of the cold injury. There are several theories on the physiology of frostbite, none of which have been adequately tested. The following theories have been proposed: (*a*) There is a vasospasm caused by cold which reduces blood flow to the tissues and causes tissue anoxia. This is the basis for the proposal that sympathetic lumbar block or section be used in the treatment of frostbite. (*b*) There is nerve damage such as axon swelling in mild cases or complete destruction in severe cases. (*c*) There is damage to the capillary wall so that the normal capillary filtration system is damaged. Fluid accumulates in the tissue spaces to such a degree that collapse of the capillaries occurs and anoxia of the tissue cells develops.

At the present time careful physiological studies are needed to determine the mechanism of cold injury. This is a field of physiology which in the past has been neglected and only a few papers have been published. The most outstanding investigation is that of Lewis & Love (54) who courageously froze sections of their own skin and noted the physiological changes which occurred.

Cold therapy for frostbite.—At the present time the popular method for treating frostbite is to apply cold in the acute hyperemic stage. This method is particularly recommended by Greene (46) and White (50) and differs from the "sound conservative

therapy" of Brahdy (55) who merely tries to prevent infection. In the cold treatment White (50) uses an electric fan or a spray to cool the warm hyperemic extremity until the skin has reached a temperature of 85 degrees F. Greene (46) recommends the use of a cabinet for the extremity to be treated in and a cabinet for this purpose is described by Bigelow & Lanyon (56). Webster, Woolhouse & Johnston (47) used ice packs. The physiological rationale for the cold treatment, as given by all who advocate this method of therapy, is obscure and is based on the belief that the tissues are suffering from oxygen deficiency. According to this theory, since the injured extremity is warm, its metabolism is increased in accordance with the Arrhenius law which states that the chemical activity is approximately doubled by a ten degree C. temperature increase. There is an increased need for oxygen due to the increased metabolism but the injured circulation is not supplying oxygen to the tissues in the amount needed. Cooling the tissue reduces the demand for oxygen, and if a hyperemic limb is cooled for a few days an improved oxygen supply can be reestablished. This theory presupposes that the cold treatment will be more effective in reducing oxygen demand of the tissues than in interfering with the processes for repairing and improving the circulation. As evidence in support of this method the experiments of Brooks & Duncan (57) have been cited who subjected rats' tails to pressure ischemia and showed that the tissues could withstand much longer pressure ischemia in a cold than a warm environment. On the other hand, the same authors (58) showed that a cold treatment of inflammation caused by an aseptic irritant postponed but did not alter the usual course of events in inflammation. At the present time it remains to be demonstrated by controlled experimentation that cold therapy does more than postpone the ordinary course of events in recovery from cold injury.

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ENERGY METABOLISM

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Not so long ago the term energy metabolism signified chiefly the energy exchanges of the entire organism, as a unit, at rest and in various other conditions. With time, energy metabolism was subjected to additional types of analysis made possible by new technics. The metabolism of organs *in situ* and of excised tissues was examined. The advance, however, did not stop at this point. Cellular metabolism is being broken down to its constituent enzyme systems, conveying energy. All these methods of analysis will finally permit us to obtain a better view of the energy metabolism of the intact organism, the original object of this branch of physiology. The subject matter of energy metabolism will be treated in the following review in the order of its development.

Basal Metabolism

Lewis and co-workers (1) have continued their researches on basal metabolism, particularly in children. In contrast to some previous observations, they found no absolute increase at puberty in the basal metabolism expressed as calories per hour per square meter of surface area. The authors do point out, however, that the rate of decline is slower at this time than in the earlier years and that this diminution in the rate of fall may be interpreted as a relative increase in metabolism during adolescence.

Because of a previous suggestion that there might be a correlation between basal metabolism and body temperature, Williams (2) studied thirty-three patients with basal metabolic rates ranging from plus 10 per cent to minus 34 per cent and within these limits did not find a relationship between basal metabolic rates and basal body temperatures, not even when thyroid was administered to the point of clinical tolerance.

In ninety-seven rheumatic children (3), the basal metabolic rate averaged minus 7.6 per cent. The values, however, approached normal from July to December but fell during the other half of the year. The authors ascribe the low basal rate to a toxic effect on the thyroid, an effect which is most intense following the season of greatest rheumatic activity.

In patients with ulcerative colitis (4) and in homosexuals (5), the basal metabolic rate and the responses to the administration of carbohydrates were found to be normal.

Newburgh (6) reviewed the results of the studies of energy metabolism in obese individuals and found that their basal metabolism is higher and that they expend more energy in work than normal people of similar age, height, and sex. Since they are not able to absorb more energy from their food, they must eat more than normal people to avoid loss of weight.

Heinbecker, White & Rolf (7) observed great obesity in dogs following destruction of centers in the base of the brain. Like Newburgh, they conclude that the changes in metabolism leading to obesity are quantitative rather than qualitative; following their operative interference the intake of food becomes excessive in relation to the bodily requirements.

In an investigation on the therapeutic action of amphetamine and propadrine in obesity, Tainter (8) administered these drugs to rats. He found that the loss of weight produced by these drugs cannot be explained either by increased metabolism or augmented activity but must be ascribed chiefly to impairment of appetite.

Weymouth and associates (9) examined the basal metabolism of the kelp crab and then on making a comparison with results from other animals came to the general conclusion that oxygen consumption maintains a simple relation to body weight. They found that the regulation of metabolism is not a function of body surface nor is it systemic, since it is operative during the survival period of excised tissues. The authors relate metabolism to concentration of cellular enzymes and believe that these enzymes maintain a power relation to the total weight of the cell.

During the last few years, data have been accumulating to substantiate the view that energy metabolism depends in part on concentration of cellular enzymes. The lower metabolism of the brain in newborns has been attributed to their sparce concentration of cerebral enzymes (10), while the higher metabolic rate per kilogram of smaller animals agrees with a correlation in which the cytochrome-*c* concentration in kidney cortex bears an inverse relationship to the body weight of some mammalian species (11). Günther (12) affirmed that body surface is one among multiple factors that determines the intensity of metabolism because basal metabolism is best expressed as a function of body weight with the exponent 0.75 and not 0.66, surface area.

Method.—In their work on children, Lewis, Duval & Iliff (13) found that the results of the first satisfactory determination of basal metabolism revealed no significant differences from subsequent determinations attributable to experience. Accordingly no practice period is prescribed, but the first determination in which the child refrains from muscular activity and is relaxed, but wide awake, is accepted as satisfactory. Contrary to the general belief, reliable determinations of basal metabolism in children under eight years of age may be procured with the bedside type of apparatus (14).

Live stock.—Brody, Kibler & Trowbridge present data for oxygen consumption and pulmonary ventilation rate in growing chickens (15), swine (16), and horses (17). In most species the metabolic rate achieves an early maximum. In chickens the metabolic peak occurs about one month after hatching; in swine, at puberty. On comparing these results with others on cattle, rats, and human beings, it is seen that the metabolic peak in cattle is observed during pubescence and weaning, since in cattle puberty coincides with weaning; in rats metabolic rates rise to a maximum some time between weaning and puberty; and in human beings, with weaning. Horses appear to be an exception to the other mammals studied, for they do not exhibit an early metabolic peak. In these animals metabolism increases until full maturity is reached and growth ceases. Horses are an exception in another way too, for their metabolic rate is no greater on standing than on lying down (17). For the conversion of food to milk in a good dairy cow about 25 per cent of the energy from the digestible food may be recovered in the milk, 33 per cent in a superior cow, values which are approximately the same as those obtained in other dairy species and in women (18).

Effects of Foods on Metabolism

Hexoses.—Determinations were made on the effects of hexoses on the respiratory exchange of man, monkeys, goats, and cats. There appears to be a species difference in the rapidity with which they are metabolized and raise the respiratory quotient. In order of decreasing effectiveness: with man (19), fructose, galactose, and glucose; in monkeys (20), glucose, fructose, and galactose; in goats (21), fructose, glucose, and galactose; while in the cat (22) the order is glucose, galactose, and fructose. Cellobiose (23), a disac-

charide produced by the hydrolysis of cellulose, is utilized in the mammalian (rat) organism.

Specific dynamic action.—Forbes & Swift (24) continued the investigations of the Institute of Animal Nutrition in the Pennsylvania State College on the associative dynamic effects of protein, carbohydrate, and fat. These workers made a study on mature albino rats of the dynamic effects of beef protein, cerelose (corn sugar), and lard, individually and variously combined and fed as supplements to a complete diet sufficient for maintenance. The dynamic effect of beef protein was 32 per cent, of cerelose 20 per cent, and of lard 16 per cent of its gross energy. On the other hand, the action of mixed supplements of protein and fat, and of carbohydrate and fat, was less even than that of fat alone. The authors justly conclude that the dynamic effects of individual foods or nutrients are without significance as constants in any mixed dietary. In further support of this conclusion, Forbes *et al.* found that in rats fed equicaloric rations, containing however either 10 per cent, 25 per cent, or 45 per cent protein, the heat production did not vary with the protein content of the diet (25).

Caffeine.—In observations made on well-trained human subjects (26), it was observed that the stimulating effects of coffee and tea on metabolism are the same as those of the pure alkaloid, caffeine, in solution.

Effects of Endocrines on Metabolism

Thyroid.—Rats were rendered hyperthyroid, and then the oxygen intake of their excised tissues was compared with that of normal controls. Liver, kidney, diaphragm, and heart showed significant increases in oxygen consumption as a result of the treatment but none was observed in spleen, brain, or testis (27). It is interesting that observations made *in vivo* in human cretins yield a different result as far as the brain is concerned, since the determination of brain metabolism which included the observation of ateriovenous oxygen differences and changes in blood flow revealed a significant augmentation in brain metabolism (28), an augmentation not necessarily reflected in improved performance (29, 30). If the administration of thyroid increases brain metabolism of the normal individual as it does that of the cretin, then it would seem that the stimulation of the central nervous system following thyroid is observed only *in vivo* and, therefore, depends in the greatest part on the organization of the individual.

Williams & Kendall (31) carefully studied two women, first for 22 days on a high thiamine diet, then for 136 days on a low thiamine diet, and finally for 81 days with increasing doses of thiamine. It was found that in the absence of thiamine, thyroid was less effective in promoting metabolism. There was some rise of blood pyruvate when both thiamine and thyroid were given, but a still greater increase occurred when thyroid was administered with a low thiamine intake. The interrelations between thyroid function and vitamin metabolism are reviewed by Drill (32).

Thyroidectomy in the adult female monkey produced effects that were slight in comparison with those seen in the human (33). This result is in agreement with others observed in experimental thyroidectomy, in which it is known, in the first place, that animals are least susceptible during the stage of active sexual life. In addition, herbivorous animals withstand thyroidectomy much better than carnivorous ones (34).

Hyperthyroidism and antithyroid substances.—An accepted viewpoint on the action of iodine in effecting a remission in hyperthyroidism is that under the influence of ingested iodine, thyroxin accumulates in the gland as its stores of thyroglobulin are augmented, and during this period less thyroxin is liberated into the blood stream. An additional suggestion for the therapeutic effect of iodine comes from the work of Morton *et al.* (35) who observed that *in vitro* formation of thyroxin was inhibited when the inorganic iodide of the suspending fluid of the thyroid slices was raised above an optimum value.

Up to the present, iodine has been used to secure amelioration of hyperthyroidism and has been regularly employed in preparation for subtotal thyroidectomy. Now with thiouracil not only are remissions more uniformly obtained but the character of the remission is more stable. In the review of energy metabolism for 1944, Kleiber (36) discussed some new antithyroid drugs which have a potent effect in decreasing energy turnover. These drugs exert their influence by stopping thyroxin formation. As a result thyroxin concentration diminishes in the blood and in response to this change the anterior pituitary elaborates additional thyrotropin which stimulates the thyroid gland to hypertrophy and hyperplasia. The normal consequences on the thyroid are a greater concentration of iodine within the gland and an accelerated production of thyroxin (37). The latter, however, becomes impossible in the presence of the antithyroid drugs, and the basal metabolic rate

unsupported by thyroxin gradually falls to a low level. The present review summarizes some of the advances made in the normal animal and human being and also in the patients with hyperthyroidism.

The new work confirms the view that antithyroid drugs interfere with the formation of thyroxin and not with the effects of that substance upon the peripheral tissues. These conclusions apply to the members of the aniline group (sulfa drugs), the thiourea group (thiouracil), and thiocyanate. The effects of the antithyroid drugs measured both by enlargement of the gland and failure to form thyroxin have been observed *in vivo* in rat, chick, rabbit, and man (38 to 42), and experiments on thyroid slices (43 to 46) also reveal inability to produce thyroxin.

Unfortunately little is known of the action by which these drugs depress thyroid function. Probably the enzymatic formation of thyroxin is interfered with. Thiocyanate inhibits the activity of the cytochrome—cytochrome-oxidase system (47), but the sulfonamides and thiouracil do not do so. Thiouracil interferes, however, with the peroxidase reaction in thyroid tissue (48). By *in vitro* experiments it has been demonstrated that thiocyanate (43) and thiouracil (46) inhibit the iodine-concentrating ability of the thyroid gland. This conclusion is in agreement with observations made *in vivo* with thiouracil but not with thiocyanate (42, 49), for the latter causes the thyroid gland to absorb more iodine than it does without the drug. Apparently additional work is required to clear this point.

With proper dosage these drugs may induce a condition of hypothyroidism and the experimental production of cretinism is reported following the administration of thiouracil to newborn rats (50). Similarly the growth of fish is stunted by this procedure (51), and the metamorphosis in tadpoles is inhibited (52).

Thiouracil is being tested in the management of hyperthyroidism. When thiouracil is given in this disease, the glandular structure of the human thyroid does not necessarily enlarge as much as that of lower animals with normal thyroids to start with; in fact, the overactive gland may even become smaller as colloid formation is depressed (53). Though occasionally complications arise (54), these are readily controlled by change of therapy and now the next step is to determine to what extent thiouracil may replace thyroidectomy. It is known that if medication is stopped soon after

a remission is obtained, the disease recurs, but if the drug is continued on a maintenance level, 0.1 to 0.2 gm. daily for a period of half a year or more, the patients have been able to retain their remission after the maintenance dose has been stopped (53). Favorable clinical reports have appeared not only in the U.S.A. (54a, 55, 56) but also in Canada (57, 58, 59) and Great Britain (60). An excellent review of the thiouracil problem has appeared in an editorial in the *Journal of the American Medical Association* (61).

Adrenal cortex.—Riddle, Smith & Miller (62) studied the metabolic rate of adrenalectomized pigeons maintained in good condition with sodium chloride and found little or no change in their heat production. There is little doubt that adrenalectomized animals not maintained in good condition by administration of salt or endocrine treatments do exhibit a fall in basal metabolic rate. The observation of Tipton (63) is of special interest in explaining the impairment of metabolism. Rats adrenalectomized and not receiving special treatment exhibited a decrease in cytochrome oxidase activity in all tissues studied and a fall in the concentration of cytochrome-*c* of kidney and liver. Treatment with sodium chloride prevented some of the decrease while adrenal extract was more effective, permitting only a slight diminution in the concentration of this enzyme.

Anterior pituitary.—A ten-day fast produced a smaller fall in the metabolism of hypophysectomized pigeons than in unoperated birds (64). Smith & Riddle interpret this smaller decrease as being due to secondary atrophy of the thyroid gland, diminishing the endogenous protein catabolism and involving a more complete utilization of the fat reserves. The operated birds thus obtained more heat from a smaller amount of their own tissue.

Exercise and Tests of Physical Fitness

Karpovich & Millman (65) studied the energy cost of swimming and found surprisingly high increases of metabolic rate during this exercise. Arranged in the order of increasing energy cost the strokes are crawl, back, breast, and side. Unskilled swimmers expended from two to five times as much energy as skilled swimmers.

In seven medical students working on a bicycle ergometer, Foltz *et al.* (66) found that though training increases ability to do work, it does not greatly augment capacity to recover from it.

Rather strangely, the better the subject felt the less his total work output.

There is some evidence (67) that thiamine requirement is raised in tropical temperatures, but the question of the vitamin B_1 need during the increased metabolism of exercise is undecided. Keys and co-workers (68) observed eight normal young men maintained on a rigidly controlled regime of diet, physical work, and exhaustive tests for forty days. During fourteen of these days, some of the subjects were placed on a diet low in vitamins, containing 0.16 mg. thiamine, 0.15 mg. riboflavin, and 1.8 mg. niacin per 1,000 kilocal. Five men received placebos during these days, while three were given abundant daily supplements. All results were in conclusive agreement that the vitamin limitation was without effect on any of the functions measured. A similar lack of effect was observed when riboflavin only was limited to 0.31 mg. per 1,000 kilocal. (69). These results are contrary to those obtained by the investigators of the Harvard Fatigue Laboratory (70) who noted, however, that their subjects were placed on a more severe thiamine restriction, did harder physical labor, and were in a colder environmental temperature.

Shock & Sebrell (71, 72) chose their experimental material in such a way as to avoid difficulties in measuring fatigue and work output and to free their observations from psychological and training factors; but in order to do so, they used perfusion instead of the intact circulation. These investigators examined frog muscles perfused with buffered glucose-Ringer's solution with and without the addition of vitamins. The muscles were stimulated electrically and their fatigue curves were graphically recorded. Thiamine and pantothenate improved the work output. Niacin and pyridoxine produced a significant effect only during the final stages of fatigue. No increase in work was observed with riboflavin.

As a measure of cardiorespiratory capacity, Kibler & Brody (73) suggest the oxygen intake per heart beat per kilogram of body weight (oxygen pulse). The value is about 0.1 in athletic men, horses, and dogs, and about 0.04 for sedentary men, sheep, rabbits, and guinea pigs. This index when measured both during rest and work yields evidence on muscular working capacity. Crescitelli & Taylor (74, 75), however, find that heart rate and blood lactate are the most reliable measures both for submaximal and maximal work and that the oxygen pulse is of value only during maximal

work and then possesses no greater significance than oxygen consumption.

Yanof (76) had healthy individuals and patients perform a moderate amount of work so that ten minutes after exercise blood lactate showed no increase over the resting value. Trained persons did not sustain a rise in blood pyruvate while untrained subjects and patients with cardiac disease or with hypertension revealed an increase of this substance.

Metabolism of Organs and Tissues

Brain.—Advances in the energy metabolism of isolated organs and tissues were made on the brain, liver, and other organs. The oxygen intake of the brain in human subjects was measured by analyzing blood samples from the internal jugular vein and from an artery for oxygen. When undifferentiated mentally deficient individuals (77), i.e., abnormal only in so far as having low intelligence quotients, were used as subjects it was found that there was a gradual increase in the arteriovenous oxygen difference from six years of age to twenty, after which the difference remained constant to old age. Without the additional determination of cerebral blood flow, cerebral metabolic rate cannot be evaluated, but if the changes in human subjects are similar to those of lower mammals (78), it would seem that the human brain metabolism rises gradually during the growth period. Patients over twenty years of age with mongolism, cretinism, and phenylpyruvic oligophrenia reveal lower cerebral arteriovenous oxygen differences than normal adults (79), and it is suggested that their brain metabolism is below the normal level.

In patients with pernicious anemia, or cardiac decompensation, low arteriovenous oxygen differences are observed indicating the brain may not receive an adequate amount of oxygen in these diseases (80). With acute destructive lesions within the brain, the arteriovenous oxygen differences may also decrease but in this case the cause lies in the affected portion of the brain which has an impaired metabolism.

In studies of excised cerebral tissues, the Q_{O_2} (81) for the rat brain is somewhat higher than that for the bass and increases with temperature to a maximum of 40°C. while in contrast the fish attains a maximum at 35°C. Although the authors point out the correlation between the results and habitat temperatures the

observations are also in accordance with the respective positions of these animals in phylogeny.

Liver.—Slices of liver taken from rats fasted for twenty-four hours and then subjected to shock as a result of hemorrhage exhibited a depression of oxygen intake (82). This depression may explain in part the increase in plasma amino nitrogen observed in these animals. The liver is especially susceptible. Excised renal tissue in contrast to hepatic is relatively unaffected by shock. It is interesting that Beecher & Craig (83) found no change in the oxygen intake of liver, brain, and heart muscle of cats also fasted for twenty-four hours and maintained in hemorrhagic shock from one to four hours. As suggested by the former group of workers (82), a smaller animal, such as the rat, with a higher metabolic rate per kilogram might be expected to yield earlier to untoward conditions after a twenty-four hour fast. The effect of anoxia on excised liver was examined by Craig (84) who found that hepatic tissue excised from fed rats and then exposed to an atmosphere of nitrogen exhibited both a higher oxygen consumption and a greater lactic acid production than did livers similarly treated but taken from fasted rats. In addition to substrate, the presence of potassium in the suspending fluid of the liver proved important for the maintenance of metabolism following the exposure to anoxia (85). Impaired hepatic oxidations have also been used as an indicator of biotin deficiency. Liver slices from biotin deficient rats revealed an increase of metabolism with either lactate or pyruvate when biotin was added. The respiratory quotient was higher, the Q_{O_2} greater, and the substrate disappeared more rapidly from the medium when biotin was added to it (86). In addition the Q_{O_2} of liver slices have been employed to elucidate the mechanism of the hyperpyrexia which sometimes follows severe burns. The lymph collected from the burned hind leg of dog (87) or calf (88) increased the Q_{O_2} of rat liver slices as compared with slices from the same liver in normal lymph. A similar stimulatory effect was observed on the Q_{O_2} of diaphragm (87).

Heart.—The respiratory quotient of cardiac muscle excised from rat varies between 0.8 and 0.9 (89), in agreement with previous observations made on frog and dog heart.

Anoxia.—To maintain life, energy must continually be made available to the cells. Whenever oxidations are not adequate, energy from anaerobic sources, chiefly glycolysis, is usually at

hand. But the brain utilizes some anaerobically derived energy, even with the plentiful supply of oxygen since the liberation of lactic (90) and pyruvic acids (91) from the brain of quietly resting unanesthetized man has been observed. If the brain acts in this way with its normal complement of oyxgen and normal oxygen requirement, then when either the oxygen supply is impaired or the oxygen requirement increased the brain might be expected to make a greater call on anaerobic sources. Such a contingency has been observed in partial anoxia (92) and in convulsions. During anoxia not only does lactic acid accumulate in the brain but phosphocreatin breaks down, changes which are reversed on readmission of air (93). When cerebral requirements are stepped up by hyperactivity caused by convulsant drugs or electrical stimulation, cerebral anoxia ensues (94) causing an increase of glycolysis and splitting of phosphocreatin but not of adenosinetriphosphate (95).

In view of the results described above it becomes important to examine further the phenomenon of cerebral glycolysis. In such studies on dogs and cats (96) the various parts of the brain were found to glycolize at different rates; moreover, the glycolytic rates of each region change with growth. In the newborn, glycolysis is most rapid in the medulla, and then recedes with increase of age. The caudate nucleus and cerebral cortex, on the contrary, are slow initially and then grow in glycolytic activity until some time before complete maturity is attained.

The quantitative relationship between the energy from oxidative and glycolytic sources has been determined on excised cerebral tissues of the rat (78). Both the aerobic and anaerobic releases are smallest in the newborn, rise to a highest rate at about fifty days of age, and then decrease somewhat to old age. During the entire lifetime, the aerobic rate is greater than the anaerobic and the difference between the two represents the calories which the brain foregoes during anaerobiosis, the "energy deficit." In general, the deficit is small in the newborn, increases with growth, and then decreases somewhat after maturity is attained. The small energy deficit in the newborn is correlated with its unusual ability to withstand anoxia and hypoglycemia (97). In the adult the greater energy deficit of the cerebral hemispheres in comparison with the brain stem is related to the susceptibility of the higher centers to anoxia and hypoglycemia (98, 99). The greater energy demands of the upper parts of the adult brain also account for the more rapid

depletion of their intrinsic glycogen stores during hypoglycemia (100).

Because the body and particularly the brain, which is most susceptible to anoxia, are able to derive energy by glycolysis, hyperglycemia produced in infant rats by the injection of glucose prolongs further their extraordinary anaerobic survival period, and conversely hypoglycemia shortens their anaerobic survival (101) as it does that of adult rats. Selle (102) further analyzed the gasping pattern of anoxic young animals and its prolongation by the administration of carbohydrates and its abbreviation by insulin hypoglycemia. The effects of various glycotropic substances on this phenomenon have also been studied (103).

From the above results on the administration of exogenous carbohydrate and the use of substances influencing blood sugar level it might be expected that well-filled hepatic glycogen deposits would be advantageous for axonic survival. In accordance with this expectation is the observation that ability of rats to withstand anoxia four to eight hours after feeding is greater than in other rats fasted from twelve to twenty-four hours (104).

Resistance to anoxia is also strengthened by diminishing energy requirements. Thyroidectomy in fed animals (105) increases the resistance to anoxia, as does the administration of thiourea and thiouracil with (106) or without (107) dilatin. On the other hand, treatment with thyroxin has the reverse effect.

For some reason (108), riboflavin given intravenously to a dog prevented the depression of the linguomaxillary reflex during inhalation of a low oxygen mixture. Similarly the contraction of excised smooth muscle was suppressed by nitrogen to a lesser degree in the presence of riboflavin. These vitamin effects, however, did not seem to influence the intact organism significantly, for large amounts of the vitamin-B complex do not ameliorate the effects of anoxia on critical fusion frequency, electroencephalogram, or pulse rate.

Nelson and associates (109) confirmed the observation that rats fed on nothing but carrots for ten days were afforded marked protection against lethal effects of a simulated altitude of 30,000 feet for two hours. Succinic acid, a breakdown product of cellulose, one of the constituents of carrots, did not afford a similar protection against anoxia (110).

Though the results of anoxia are first apparent in the reactions

of the central nervous system, probably most organs of the body are influenced in an adverse manner. Rats exposed daily to a small concentration of carbon monoxide grew normally and had a normal incidence of pregnancy; however, there was a tendency towards abortion, the average size and weight of the litter was subnormal, and the mothers failed to nurse their young (111).

Atabrine is known to possess toxic effects, some of which diminish the efficiency of aviators. The observations of Wright & Sabine (112) help to clarify this problem, since they found that the oxygen consumption of rat brain, liver, and kidney slices is inhibited by atabrine. This inhibition is especially dangerous for aviators, since the oxidation of the cerebral substrates, glucose, lactate, and pyruvate, is prevented, an action which is synergistic with anoxia. Haas (113) has shown that the atabrine inhibition is especially effective on the enzymes cytochrome reductase and glucose-6-phosphate dehydrogenase. The drug competes for the protein moiety of these enzymes and their consequent inactivation is a cause of its toxicity to man and to the malarial parasite.

Effect of carbon dioxide on respiration.—It is well-known that the inhalation of carbon dioxide stimulates pulmonary ventilation, but after a certain maximum effect is obtained any further increase in the concentration of carbon dioxide brings on a depression of respiration. "It is no novelty to state that carbon dioxide has narcotic powers" (114). Respiratory studies on tissues have thrown light upon the mechanism of carbon dioxide depression. In the case of excised retina (115), a rise in carbon dioxide from 1 to 5 per cent at a constant pH nearly doubled respiration and glycolysis. When carbon dioxide was increased to 20 per cent no additional effect was observed on glycolysis but oxidations were depressed. Similarly in a study of feline excised cerebral cortex and medulla oblongata maintained at a constant pH, an increase of carbon dioxide from 1 to 5 per cent doubled glycolysis of both tissues but did not alter their respiration (116). A further augmentation of carbon dioxide to 20 per cent did not influence glycolysis nor oxidations in the cortex but did impair oxidations in the medulla.

Oxidation of fat.—In the processes by which fats yield energy, two-carbon fragments are prominent. Deuterio acetyl groups were excreted by rats fed labelled butyric, n-valeric, and myristic acid (117). The relationship between the two and four carbon chains appears to be reversible, for the two-carbon fragments formed in

the oxidation of fat may be condensed to ketone substances in slices of liver (118). In this organ, the production of ketone substances is under endocrine control, for it is accelerated by anterior pituitary extracts (119). Both the two and four-carbon chains may be oxidized. Slices of kidney, but not brain, oxidize acetic acid (120). Kidney is also able to oxidize a number of four-carbon monocarboxylic acids (121), and an enzyme has been extracted from liver which facilitates the oxidation of butyric acid (122). Probably the Krebs cycle is involved in these oxidations. It is suggested that acetoacetate is an intermediate in the transformation of carbohydrate to fat (123), and there are additional data indicating that two-carbon chains may be synthesized to form fat (124). The question of the oxidation of lipids was investigated but not from the point of view of two-carbon chains by Elliott & Libet (125) who studied the autoxidation of purified mixed phospholipid, which occurred at significant rates only in the presence of inorganic iron and ascorbic acid.

Method.—Stadie & Riggs (126, 127) described a respirometer for the determination of the gaseous metabolism of surviving tissues at high pressures of oxygen and also a microtome for the preparation of tissue slices for metabolic studies.

Excised kidney cortex and liver, but not cerebral cortex, reveal a higher oxygen consumption if prepared for observation at 10°C. than at 35°C. (128).

Energy Containing Phosphate Bonds

The importance of organic phosphate bonds as stores of energy has been emphasized by Lipmann (129) who described a phosphate cycle beginning with inorganic phosphate compounds with no readily available energy. The introduction of inorganic phosphate into ester linkage, however, absorbs about 3,000 cal. per mol., energy available when the ester linkage is broken. More important are the compounds with energy-rich phosphate linkages containing about 10,000 cal. per mol. Phosphocreatin and adenosinetriphosphate are such structures. These linkages are built by the energy obtained either from oxidations (130, 131) or glycolysis. Energy from phosphocreatin passes on to adenosinetriphosphate which in turn yields it for various biological purposes. The terminal phosphate group is the one most frequently split off (132). Phosphate-bond energy is intimately connected with the sudden release of

energy which must be available in muscular activity. The phosphate cycle has been elegantly demonstrated by Furchgott & Shorr (133) for cardiac muscle and by Kalckar and co-workers (134) for voluntary muscle. Bollman & Flock (135) have found that on occlusion of the blood supply to rat leg muscle its organic phosphate compounds are hydrolyzed to yield inorganic phosphate, an effect which may be reversed if the flow of blood is restored within three hours.

Another use of phosphate-bond energy has been observed by Nachmansohn and associates (136, 137) who studied the system for the synthesis of acetylcholine, the substance involved in the transmission of the nerve impulse. They find an enzyme, choline acetylase, which is active only in the presence of adenosinetriphosphate. They showed further that the energy-rich bond of adenosinetriphosphate is supplied by the breakdown of phosphocreatin. Because of the importance of the subject it is interesting that we now have additional evidence on phosphate metabolism in human muscle and brain (138).

The coupling between phosphorylations and oxidations indicates not only that energy which is stored by oxidations may be released anaerobically, but that phosphates take part in the oxidation of substrates. Phosphate is concerned not only in the oxidation of glucose but also of fructose (139) as well as pyruvate. The method of oxidation of pyruvic acid has not been entirely elucidated, a modified Krebs cycle and the intermediary formation of acetoin being two of the suggestions. In the intact organism evidence has been obtained by the oxidative decarboxylation of pyruvate to acetyl (117). It is interesting to observe that *Escherichia coli* (140, 141) and *Bacillus acidificans longissimus* (142) contain enzymes which catalize in a reversible manner the phosphoroclastic splitting of pyruvic acid to acetylphosphate.

The conception that phosphate plays a role in oxidations not only applies to carbohydrate but also to fat. Liver homogenates were able to oxidize four to eighteen-carbon saturated fatty acids (143). The failure of previous investigators to demonstrate the oxidation of higher fatty acids has been overcome by adding to the homogenate cytochrome and adenosinetriphosphate or compounds capable of phosphorylating adenylic acid.

Finally phosphates are involved in foodstuff transformations. The livers (144) of rats fed galactose showed an increase not only

of galactose-1-phosphate but also of glucose-1-phosphate. The authors describe this transformation as the mechanism for the conversion of galactose to glucose. In the muscles of frogs (145), but not in those of cats, glucose and fructose-6-phosphate are interconvertible.

Insulin.—Previous work on the influence of insulin on phosphate metabolism has been reviewed by Stadie (146). The recent investigations show increases in organic phosphates following administration of insulin and glucose. Resting muscle exhibits a rise of adenosinetriphosphate and phosphocreatin (147) and also of hexose monophosphate (148). The last substance also increases in the blood. The liver reveals an accumulation of adenosinetriphosphate (149). The mechanism by which insulin facilitates such changes is, however, undisclosed by these investigations.

Method.—A schema for the determination of the acid-soluble phosphorous compounds of cerebral tissue has been made by Stone (150). Kalckar (151) writes on an enzymatic method by which the two terminal labile phosphate groups of adenosinetriphosphate can be separated and LePage (152) discusses substances interfering in the determination of phosphoglycerol. A detailed account on the methods for the determination of phosphates is presented by Umbreit (153).

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THE PERIPHERAL CIRCULATION

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Certain phases of the physiology of the peripheral circulation have been reviewed recently in considerable detail (1 to 6). These reviews are listed separately with their titles in the bibliography but will also, in some instances, be referred to in the text under appropriate headings.

Physical factors concerned in the peripheral circulation.—The arterial pressure pulse assumes its simplest form in small animals in which diastolic pressure falls smoothly (7) whereas in dog and man superimposed reflected waves of arterial origin make the pressure curves more complex as well as different from artery to artery. Peripheral resistance also modifies the contour of these superimposed waves which may therefore indicate the presence of peripheral vasodilatation. To measure peripheral resistance in dogs Wiggers (8) has improved the method of Stewart by which the Fick principle is applied to the infusion of sodium chloride solution into the heart. Repeated measurements are possible and greater accuracy is obtained. Depending on body size average values of 4,230 to 5,570 units were observed. In this connection it is interesting that with certain assumptions (9) the E/W ratio of Wezler & Böger can be derived approximately from heart rate and blood pressure measurements alone. The following deviations from the normal ratios of 0.79 to 0.98 are given: subcutaneous epinephrine, 1.34; pyrotherapy, 2.56; exercise, 4.04; and pitressin, 0.59. The flow of blood between cognate and collateral arteries has been compared by simultaneous perfusion at the same and different pressures (10). Resistance to flow in anastomatic channels is low compared with the cognate bed; vasoconstriction influences both sets of vessels.

Shipley & Gregg (11) find no justification for the contention that a rather marked degree of constriction is required to produce a significant reduction in flow through a vessel. The effect of external pressure is related to the axial length of the constricted area, the velocity of flow, and the viscosity of blood. Even slight compression, as in a thermostromuhr, may have a variable and unpredictable effect on blood flow. It has been claimed that edema

fluid may interfere with blood flow but this disadvantage must be very slight since peripheral blood flow in cardiac edema is normal or possibly increased (12). The optimal external pressure to produce the sign of Traube and the Duroziez murmur has been defined with an analysis of the mechanism by which these signs arise (13).

The formation of bubbles in blood vessels at low atmospheric pressures has been studied by physical (14) and *in vivo* (15) methods by Harvey *et al.* Bubbles do not form, even at very low pressures, in single living cells, though they may appear inside dead or injured cells, as well as in blood vessels or lymphatics as a result of muscular contraction. Bubbles may arise *de novo* or from "gas micronuclei" which are attached to or form on, the walls of the blood vessels where, under proper conditions, they grow and finally break loose. The pulmonary capillaries effectively filter out gross air bubbles and nuclei. Intravascular bubbles are far more numerous in vessels traversing tissues rich in fat (16).

The mechanical effects of respiration on arterial blood pressure in man are variable depending on the rate, depth, and nature of respiration (17). Ordinary quiet inspiration produces generally a fall, expiration a rise, of arterial blood pressure, but abdominal breathing may produce the opposite effect. Coughing (17, 18) and straining (18) may produce large temporary elevations of arterial blood pressure and venous pressure. Breathing against pressure in the anesthetist's airway elevates venous pressure, while reducing arterial pressure and arterial blood flow (19).

Nervous control of peripheral circulation.—According to Bülbring & Burn (20) the pressor response to splanchnic stimulation is increased by constant infusion of epinephrine into a spinal cat, and decreased by a single large dose of epinephrine. It is shown that the transmission of impulses through sympathetic ganglia is facilitated by small doses of epinephrine and depressed by large doses.

The pressor and depressor reflexes produced by stimulating the cat's posterior tibial nerve appear to traverse separate afferent nerve fibers which differ in their responses to the strength, duration, and frequency of stimulation, and to local nerve block by cocaine, cold, or asphyxia (21). Irrespective of changes in blood pressure diverse sensory stimuli initiate vasoconstriction in the cat's paw; the latent period, duration, and central reflex time of

these reflexes are given (22). The central pathways for these reflexes are complete below the level of the anterior corpora quadrigemina (22), while the centers essential for the pressor response to increased intracranial pressure extend to the level of the inferior olive (23). Wiggers *et al.* (24) in transecting the spinal cord found no impairment of venous return which could be ascribed to extravascular causes such as reduced tone of skeletal muscle. The reduction in blood pressure is due chiefly to arteriolar dilatation, without impaired venous return. Denervation of the rabbit's ear reduces the dose of epinephrine required for full constriction (25) but does not affect the action of ephedrine, pitressin, and ergotoxine significantly. Essex *et al.* (26) have found that ten years after unilateral lumbar sympathectomy one dog exhibited almost equal blood flow on the operated and unoperated sides, with increased reaction to epinephrine, and resistance to histamine, on the sympathectomized side.

Changes in blood pressure, associated with Traube-Hering waves have been measured directly in man (17) and in the hind leg of the dog (27) where they recur in cycles of about 17 sec. and indicate a change in vasomotor tone of 1.7/1. Spontaneous vasomotor variations in the volume of the fingertips can be classified into major and lesser types, and related to the emotional status of the subject (28). Spinal anesthesia modifies this pattern by producing wide dilatation of the cutaneous vascular bed of the lower extremities and, secondarily, a compensating constriction in the upper extremities (29). Other observations on vasomotor responses in man deal with the differences in vasoconstrictor tone indicated by the ease of producing indirect or reflex vasodilatation by heat (30); circulatory collapse, syncope, and arterial constriction during arterial puncture (31); vasomotor reactions to local injury and thrombosis (32); the relation of age to the rise in blood pressure produced by immersing one hand in ice water (33); evidence of vasoconstrictor tone in the blood vessels supplying the muscles of the forearm (34); and the level at which vasoconstrictor fibers to the human forearm emerge from the spinal cord (35).

The removal of the carotid sinus in dogs under chloralose reduces blood pH by 0.05 to 0.12 with evidence of both gaseous and metabolic acidosis (36). Section of all four moderator nerves in stages produces in dogs an acute rise of blood pressure after the re-

moval of the last nerve, the order of section being of no significance (37). The acute hypertension is followed shortly by a chronic hypertension, which is completely different from the renal type and is characterized by great and correlated variability of heart rate and blood pressure. Prolonged stimulation of the depressor nerves in the rabbit may lower blood pressure conspicuously for four to nine hours before hemodilution, anoxia, and damage to the vasomotor system result in death. Depressor reflexes elicited by stimulating somatic nerves are of small magnitude comparatively and of brief duration (38).

Sensitivity of the human carotid sinuses to digital pressure differs widely on the right and left sides (39). Paredrine prevents the fall in blood pressure but slowing of the heart persists though in less intense form. The occurrence of syncope in the absence of circulatory changes is verified.

Chemical factors affecting peripheral circulation.—The effect of epinephrine on the transmission of impulses through sympathetic ganglia has been mentioned (20). From perfusion experiments it is concluded that cocaine interferes with the inactivation of epinephrine, and also of sympathin, in tissues (40). A series of isothiourea derivatives (41) have been studied with respect to their effects on blood pressure, their direct action on perfused vessels, and their enhancing the constriction produced by epinephrine in intact animals and perfused limbs. The effect of sodium bisulphite on the toxicity of subcutaneous and intramuscular, but not intravenous, epinephrine is ascribed to local increase of speed of absorption (42).

Epinephrine injections into the splenic artery in man prior to splenectomy increased the concentration of erythrocytes in splenic venous blood, which fact suggests that a partial separation of cells and plasma exists (43); the expelled erythrocytes are more fragile and more spherical. In man the general vascular responses to intramuscular injections of ephedrine and epinephrine are variable though on the whole vasodilator effects predominate over vasoconstrictor effects, and average peripheral resistance is unchanged or decreased, while venous pressure rises owing to a discharge of blood reservoirs (44). Paredrinol also elevates venous pressure, but the peripheral vascular bed appears to be the chief site of action (44). The lack of pressor effect by paredrine in some medical condi-

tions remains unexplained. Except for tuberculosis, infection *per se* is not responsible for this reduced activity (45). The pressor action of optical isomers of certain sympathomimetic amines (46) and of certain volatile amines (47) are compared.

Histamine, subcutaneously injected in unanesthetized, normal dogs, reduces arterial and venous blood pressure with conjunctival and cutaneous vasodilatation and marked tachycardia, despite which the animals remain alert, active, and thirsty (48). Prior splenectomy leads to a quicker drop of blood pressure and slower recovery. Etherized animals suffered less reduction of blood pressure but did not survive as long as unanesthetized animals. No evidence of increased capillary permeability was found in these observations (48) nor when histamine in cottonseed oil was used to produce slower absorption, except occasionally in the late stages of protracted hypotension (49). Methyl cellulose and S-methyl isothiourea combat the effects of histamine while the common pressor substances are less effective (50). Histamine is liberated during protracted saline perfusion of the isolated lung at 43° C. but not at 41°C.; vigorous ventilation even with oxygen increases the histamine output (51).

The process of blood coagulation liberates histamine and one or more substances which contract many types of smooth muscle (52, 53). When perfused tissues, and particularly the rabbit's ear, are used for the purpose of detecting special vasoconstrictor substances in the circulating blood it is imperative to avoid coagulation. "Preheparinization" of the donor animal is required if the tone of the vessels of the perfused ear is to be reasonably low. Serum is completely unsatisfactory for such assays in the rabbit's ear (54).

Desoxycorticosterone acetate raises the blood pressure after adrenalectomy but does not affect the hypotension that follows hypophysectomy, though adrenal cortical extracts produce partial recovery of blood pressure (55). In hypertensive rats whose blood pressure has been reduced by hypophysectomy, purified adrenocorticotropic hormone restores hypertension to the pre-hypophysectomy level whereas lactogenic hormone does not (56). The posterior pituitary is not necessary for the maintenance of renal hypertension (57). The lowering of blood pressure by carbon arc illumination is diminished or prevented by desoxycorticosterone acetate or adrenal cortical extract (58). The transient lowering of

blood pressure produced by the oxytocic fraction of pituitary preparations differs in degree and mechanism according to species (59, 60). In human beings pituitary extracts and ergot preparations may produce asphyxia of the infant through the effect of uterine contraction on maternal effective placental arterial pressure (61).

Injected diethylstilbestrol is said to raise blood pressure of normal rats and to depress that of hypophysectomized rats (62), while no effect was observed with oral administration (63). The normal estrus cycle of the rat is associated with characteristic histological changes in the capillaries of the ovary associated with greater permeability to India ink particles after ovulation without evidence of endothelial discontinuity (64).

Moe *et al.* (65) observed that veratridine produces an abrupt fall in blood pressure due partly to bradycardia and partly to neurogenic vasodilatation of the vascular tree. These changes are mediated partly by afferent fibers in the vagus; vagotomy reduces but does not abolish this vasodilatation. Morphine increases blood flow to the hand in normal subjects, addicts, and postaddicts, apparently by reducing sympathetic activity (66). Strychnine does not affect blood pressure until convulsions appear but then mechanical effects from increased muscular tone and intra-abdominal pressure may produce marked cardiovascular stresses (67).

Renin and angiotonin in dogs elevate venous pressure and always increase total peripheral resistance, though this may be masked by cardiac weakening. It is suggested that tachyphylaxis may therefore be only partly the cause of diminishing effect from repeated doses (68). The actions of renin and the question of its relation to hypertension have been reviewed in the light of recent work (69, 70). In human beings renin is found in the blood of patients with eclampsia and severe glomerulonephritis, but not in the milder toxemias of pregnancy, mild acute glomerulonephritis, nor chronic hypertension (71).

A number of drugs reputedly useful in lowering blood pressure in hypertension have no effect when studied critically (72). The previously described effect of vitamin-A concentrates is uncertain and apparently due to some other and unknown constituent (73). The antihypertensive effect in dogs of partially purified hog renin is greater than that of highly purified renin, which makes the role of an antirenin unlikely (74). The importance of an antipressor

mechanism in the normal kidney is reaffirmed but the amount of active antipressor material in kidney extracts is so small that it does not appear to offer any practical therapeutic approach (75, 76). Many tissues contain protein material which reduces the blood pressure of hypertensive rats for ten to twenty days, but no longer even with sustained administration (77). Abscesses arising from transplanted kidney tissue appear to lower blood pressure more than do abscesses from other transplants (78). Additional substances tested for antipressor activity include vitamin-K preparations, which do not act uniformly (79); adrenochrome derivatives (80); pentobarbital, which in anesthetic doses reduces hypertension of long standing, but not that of recent origin (81); and yohimbine, also effective only in hypertension of long duration (81). High plasma concentrations of sodium thiocyanate reduce the rise of blood pressure produced by a given dose of crude renin (82).

Arteries.—The diameter of excised arterial segments, e.g., femoral and popliteal, decreases slightly as temperature is raised from 5° to 45°C. resembling in this respect the previously described effects of temperature on connective tissue and muscle (83). Contractions induced by stress have been used to identify and measure conduction along the wall of excised arteries (84); figures are given for latency and duration of contraction as well as of conduction rate. The general subject of arteriosclerosis and lipoid metabolism has been reviewed in detail (6).

Arterial blood pressure.—Direct blood pressure readings from the carotid artery of the rat have been compared with indirect plethysmographic readings from the tail using occluding cuffs of various sizes (85). With the very important assumption that blood pressure is identical in the carotid and the considerably smaller caudal artery, it is recommended that a narrower cuff be used for the indirect method or that a systematic correction be applied. A technique for measuring mean systolic pressures during activity, rest, and sleep has been suggested (86). The factors concerned in indirect sphygmomanometry have been reviewed with graphic registration and comparison of the criteria used in the estimation of blood pressure by the palpatory, oscillographic, and auscultatory methods (87). If the ordinary pneumatic cuff commonly used for determining brachial blood pressure is applied to the leg the average readings are higher than those for the brachial artery by

36 mm. Hg systolic and 21 mm. Hg diastolic (88). These values, as the authors state, are only relative since the cuff is too narrow for accurate measurement in the leg. The magnitudes of the differences observed were directly related to the relative circumferences of the arm and leg.

High protein diet and large doses of urea have no significant effect on the blood pressures of normal and hypertensive dogs (89). Human systolic and pulse pressures increase with advanced age, the diastolic pressure remaining constant or even falling slightly (90). The concentration in blood of sulfocyanates, though greater in smokers, has no consistent relation to blood pressure (91). The mechanical effects of respiration on blood pressure have already been mentioned (17, 18, 19).

Blood flow in various tissues.—The present status of knowledge concerning cerebral circulation, normal and abnormal, has been covered in an excellent symposium which compares critically the methods used for determining blood flow and calls attention particularly to great anatomical differences in the cerebral vascular system of various species (1). Progressive ligation of the arteries supplying the head of a dog produces a moderate and somewhat variable hypertension (92).

Peripheral blood flow in dog's muscle is on the average four times that for an equal weight of skin (93). An equation relating perfusion pressure and flow, and a unit of peripheral resistance are described. The peripheral blood flow for healthy males in the third decade averages 52 cc. per square meter per minute at 25°C., and 73 cc. per square meter per minute at 27°C. (94). Wide variations are usual, however, not only from subject to subject but in the same subject on the same day. The period required for the circulation in the forearm to reach equilibrium at various temperatures is indicated by the studies of Barcroft & Edholm (95). At 13 to 35°C. flow decreased slightly during two hours; at 37 to 42.5° maximum blood flow was attained in one hour and then followed by steady decrease, and at 45°C. flow increased to a maximum in thirty to forty-five minutes, remaining constant thereafter. When the hands are immersed in water ranging from 5 to 25°C. the skin temperature approaches that of the water most closely at 12 to 20°C., becoming increasingly warmer than the surrounding water as the bath temperature is changed to levels below or above 15° (96).

Blood flow is minimal in the range between 15 to 20°C. becoming higher as temperature falls below 10° owing, in all probability, to the liberation of dilator substances as suggested by Lewis. The general subject of blood flow in the extremities of man in health and disease is covered in a recent monograph (4).

Thiamine deficiency in man does not produce any vasomotor disturbance as measured by skin temperature and by rates of cooling or warming (97). The cutaneous vasodilatation of nicotinic acid is not associated with change of metabolic rate or body temperature, which fact suggests a direct action on arterioles of the skin (98). The decrease in cutaneous blood flow associated with smoking cigarettes has been verified (99, 100) though the detailed explanation of this effect is still not generally agreed upon. Anemia increases the blood flow to the forearm, with low normal or decreased rates in the hand (101). Peripheral blood flow in the upper half of the body is increased and variable in coarctation of the aorta (102). The effects of edema (12) and high intrapulmonary pressure (19) have already been referred to. Anesthesia in dogs requires the observance of very long control periods for quantitative studies on cutaneous blood flow (103). In man, however, local or general anesthetics produce complete dilatation of the cutaneous vascular bed as soon as light surgical anesthesia, corresponding to the first plane of the third stage, has been attained (104).

Ischemia of exercising muscle produces pain not by lack of oxygen, nor by accumulation of the usual metabolites, but probably by the liberation of potassium (105). The blood pressure rises markedly during artificially induced pain of claudication; heat accelerates, cold delays, the appearance of pain. The blood supply to the popliteal nerve of the cat offers a wide margin of safety far beyond the requirements for maintaining conduction (106). Even in the absence of intrinsic blood supply diffusion from adjacent tissues can prolong survival. The anatomical distribution of lateral and longitudinal vessels affects the survival time when blood supply is interrupted by ligation or by a tourniquet in different positions.

Capillary contractility, pressure, permeability, and fluid movement.—Clark & Clark observed previously that the longitudinally arranged adventitial cells are potential contractile elements in that they can divide and transform into circularly arranged smooth

muscle cells on developing arterioles. Contractility of capillary endothelium is present in annelids and lost in mammals, with the amphibian occupying an intermediate position. The various mechanisms which passively change capillary diameter are discussed (107). In the anesthetized monkey epinephrine, pilocarpine, and ergot produce narrowing of capillaries at the base of the finger nail while atropine, nicotinic acid, and acetylbetamethylcholine produce widening (108). The liver sinusoids of the frog and rat exhibit increased circulatory activity with glucose and thyroxin, whereas epinephrine produces constriction and acetylcholine is inactive (109). Ergotamine in patients with migraine is said to modify the "blurring" of skin capillaries which is associated with headache (110). Sympathectomy elevates capillary blood pressure in Raynaud's disease and direct microinjection measurements indicate that the gradient of pressure drop, small before operation, is increased after operation (111).

The availability of radioactive sodium has made it possible to study further the rapidity with which the sodium ion passes from the circulating blood into certain extravascular compartments. After intravenous injection the concentration of radioactive sodium in the aqueous humor of the eye reaches 75 per cent of plasma concentration in forty-five minutes and attains equilibrium in slightly over an hour (112). Equilibrium between sodium in cerebrospinal fluid and blood is reached more slowly. The rate of passage is slower in unanesthetized animals. Sodium transfer per unit weight of placenta increases as gestation proceeds; the increase in number of villi and thinning of their walls offers a morphological reason for this change in rate of transfer (113).

The permeability of the capillaries in the forearm and hand to protein is increased by the intra-arterial injection of histamine whereas simple occlusion, shock, and acute infections have no effect (114). As mentioned above (48, 49) subcutaneous histamine in dogs produces no, or very late, general change in capillary permeability but the concentration coming in contact with the capillary wall is probably less. Venous congestion of the extremities for twelve hours produces enough edema fluid to permit direct sampling and analysis of protein content. Such edema fluid from normal subjects contains 0.4 to 1.3 gms. per cent of protein, averaging 0.8. Lower concentrations of protein are found in the edema fluid

of cardiac failure and in anoxemia, fever, and infection (115). These studies indicate that there is no increase in capillary permeability to protein during anoxemia in man, or in heart failure.

Capillary permeability is said to be increased in myxedema because of greater penetration of fluorescein into the skin after intravenous injection (116) as measured by a special device for detecting fluorescence of the skin (117). Fluorescein penetration is normal in cardiac failue with edema and in cirrhosis of liver with edema; it is increased in severe vitamin deficiency with edema and in inflammatory reactions (116). Acid aniline dyes intravenously injected into guinea pigs stain selectively the inner surface of abdominal skin (118); selective permeability to acid dyes is suggested.

Subcutaneous edema, hydremia, and correlated changes in concentrations of serum proteins and chlorides are found in rats and monkeys exposed to cold environments and then rewarmed (119). Pentobarbital anesthesia of dogs reduces lymph flow by 50 per cent whereas ether increases it by 50 per cent, local anesthesia being used as a standard of reference (120). This observation explains the finding that pentobarbital sodium in sedative doses reduces the loss of fluid and protein from burned surfaces whereas morphine has no effect (121). It is suggested that this action may be due either to reduced capillary filtering surface, or to a reduction of capillary pressure, the first possibility being the more likely. Vitamin-B deficiency in the rat has no effect on the total water content of the body or of the tissues separately (122), when total food intake is kept constant.

Abnormal capillary fragility, found in 50 per cent of newborn infants within the first twenty-four hours, falls rapidly to 16 per cent mildly positive after the fourth postnatal day (123). Hereditary bleeding tendency in swine appears to consist of a double defect, namely a fault in coagulation and a failure of injured blood vessels to constrict (124). Crude hesperidin is said to protect normal animals against the pulmonary hemorrhage produced by explosive decompression (125), while a related flavone glucoside, rutin, is said to decrease capillary fragility in some hypertensive subjects (126).

Venous pressure, circulation time.—Starr *et al.* (127) have developed further the concept that right ventricular failure does not *per se* elevate venous pressure. Injuring the right ventricle of dogs

by heat in acute experiments and by ligating branches of the right coronary artery in chronic experiments, fails to elevate venous pressure to the levels characteristically found in human cardiac failure. Warren & Stead (128) describe the elevation of venous pressure and the production of congestive failure by ingestion of sodium chloride and water. Slightly different hypotheses are developed in these two papers but they agree in concluding that venous pressure is related not to right ventricular failure *per se* but to the increased blood volume found in cardiac disease. Eichna & Taube (129) state that intravenous digoxin and oubain produce striking and rapid reduction in venous pressure sometimes preceding the onset of diuresis, but not dependent on slowing of ventricular rate, on the initial level of venous pressure, or on the degree of congestive heart failure.

The effects on venous pressure of coughing, straining, and breathing against pressure have been described above (18, 19). Venous pressure is sometimes elevated by pleural effusion and, even when normal, is reduced slightly by thoracentesis; circulation time is not affected (130). The effect of positive and negative intrathoracic pressure on peripheral venous pressure in man, according to Holt (131), indicates that the latter is a function of right atrial pressure when the subject is supine, with the arm below heart level and when intrathoracic pressure is not extremely low. When the hand is above heart level, when intrathoracic pressure is very low, and when the subject is in the sitting position, collapse of the veins tends to make peripheral venous pressure independent of atrial pressure. Ryder *et al.* (132) also stress the importance of the collapsibility of veins in interpreting the significance of venous pressure. It is suggested that the measurement of local venous pressure in freely collapsed veins offers a means of determining tissue pressure at the point of collapse.

Additional figures are given for the reduction of venous pressure produced by trapping blood in the extremities (133), for the rise of venous pressure in arteriovenous fistula (134), and for the effects of venous congestion on blood flow in the extremities (135). Venous pressure remains constant at altitudes up to 40,000 feet (136). Wood & McKee describe a simple method for the continuous graphic recording of direct venous pressure in man (137).

The relation between venous pressure and intramuscular pres-

sure has been recently reviewed (2). It appears to depend upon the tightness of the fascial covering of the muscle studied (138). When the fascia is loose congestive heart failure and elevating venous pressure fail to affect intramuscular pressure; the energy of the venous bed is not transferable to the muscle mass. Intravenous injection of human plasma elevates intramuscular pressure and venous pressure (139).

Circulation times, measured in duplicate, show wide variations which indicate that significance can be attached only to marked differences (140). Using a histamine wheal in conjunction with intravenous injection of fluoroscein produces a more brilliant end point for measuring circulation time (141). Figures for "slowest circulation time" determined by having subjects breathe an acetylene-air mixture, with analyses of successive samples of inspired air, are lower than normal in thyrotoxicosis, exercise, fever, and advanced anemia (142).

Effects of posture.—The circulatory and mechanical effects of vertical stance have been reviewed in detail (1). In the dog the vertical position produces in addition to the usual hypotension and hemoconcentration a reduction of venous oxygen tension and increased sensitivity to hemorrhage (143). Increased volume flow of lymph and higher protein content suggest increased capillary permeability. In rabbits, despite circulatory changes and hypoxia, no change in the specific gravity or plasma protein content of plasma occurs (144). In cats evisceration diminishes circulatory compensation in the foot-down position but does not abolish the fall in blood pressure; hepatectomy, on the contrary, almost abolishes the hypotension (145). It is concluded that collection of blood in the liver, not in the general splanchnic region, reduces blood pressure in the foot-down position. In rabbits, first chilled then put in the upright position, deleterious effects are produced by blood loss, decreased salt intake, sodium nitrite, and infection (146); paredrinol, ephedrine, coramine, ascorbic acid, and thyroid are beneficial.

Reduction of the volume of blood in the lungs is regarded as the cause of the increased vital capacity (147) and reduced carbon dioxide tension of alveolar air (148) in the standing subject. In man circulatory adjustment during standing has been studied under ordinary conditions (149, 150), during the first few days of exposure

to hot environments (151, 152, 153), and after extensive sympathectomy (154, 155). From studies of patients with known cardiovascular disease it is concluded that the Schneider index makes very slight demands on cardiovascular reserve (156).

Blood and plasma volume.—The T-1824 method has been used to determine normal blood and plasma volumes in rabbits, dogs, goats, horses (157), and in growing rats (158). The values vary with body weight rather than area (157) and in rats with age, in that unit plasma volume attains a maximum value at an earlier age than does unit cell volume (158).

In dogs dehydration reduces plasma volume disproportionately when sodium chloride as well as water is lost (159). When human beings on a salt-poor diet are given daily ammonium chloride in addition, plasma volume is diminished conspicuously at first but shows a tendency to return toward normal when this regimen is continued for eight or nine days (160). Mercupurin diuresis in nonedematous subjects reduces plasma volume by 15 per cent with a reduction of venous pressure and pulse pressure (161). On the contrary, administration of sodium salts can increase the plasma volume by approximately the same percentage, which fact indicates that plasma volume can be regarded as constant only under relatively uniform conditions (162).

The effects of intravenous injections of normal saline and 5 per cent glucose on the volume of plasma and the concentration of plasma proteins indicate that no protein is lost in the process of distributing the added fluid (163). Normal and concentrated plasma injections produce an increase in blood volume which, while proportional to the amount of protein injected, still falls short of the full theoretical effect, suggesting some deposition of protein (163).

T-1824 in very large doses, much in excess of those used routinely in man, is toxic for dogs and cats (164). Modified methods permit the analysis of T-1824 in hemolyzed (165) or turbid (166) plasma.

Hemorrhage and shock.—In a strict sense and under ordinary conditions these two disorders should probably not be considered together. The stimulus of war has led, however, to a large number of comparative studies on the effects of whole blood, whole plasma, fractions of plasma, and various simpler substitutes in severe

hemorrhage, traumatic shock, and burns. To separate rigidly into several categories the exploratory work done on newer infusion materials in the past year would be not only extremely difficult and lengthy but, in the main, confusing. In addition a reexamination of older hypotheses in the light of new evidence has questioned the importance in shock of a general increase in capillary permeability in regions distant from the point of injury while emphasizing the role of local increase in capillary permeability and resulting gross reduction in effective blood or plasma volume. The problem is still far from solved as recent brief reviews indicate (167, 168, 169).

In tourniquet shock of dogs the amount of fluid lost locally exceeds the decrease in plasma volume and the amount of protein accumulated locally slightly exceeds the amount lost from the blood stream (170). Fluid loss from capillaries over the rest of the body is excluded by these observations which also indicate that the fluid which enters the circulation must be poor in protein. Moreover preventing local loss of fluid prevents shock, and fluid is actually added to plasma as a compensatory adjustment. In simple hemorrhage overcompensation may result (171). Related to this also is the observation (172) that increasing the interval between bleedings increases relative survival in that the total amount of blood removed can be increased. From changes in red cell volume it appears that at least two hours is required for significant hemodilution and when this occurs there is evidence that albumin is added and that globulin is not restored.

When the volume of extravascular fluid is increased greatly by administering large volumes of physiological salt solution to the point of marked edema, circulation in animals traumatized by tourniquets is maintained at a more normal level. An early cessation of infusion leads to rapid decrease in plasma volume (173). Apparently edema tends to maintain blood pressure and to prevent hemoconcentration even when the plasma protein is 50 per cent below normal level. It is concluded that the quantity and pressure of extracellular fluid is as important in determining plasma volume as is the amount of plasma protein (173). On the other hand it is noted briefly (174) that chronic hypoproteinemia in dogs increases their susceptibility to shock from hemorrhage and that this susceptibility may persist even after the serum protein has returned to normal.

The part played by blood loss in various forms of experimental shock is not always easy to evaluate. Rats exposed to trauma from the baffles of a rotating drum suffer direct trauma to the viscera, intestinal hemorrhage being more frequent in those showing the greater decreases in plasma volume (175). The changes in responses of the minute vessels resemble in many ways those seen in simple hemorrhage, ending finally with hyposensitivity, packing of erythrocytes in the capillaries, and absence of vasomotion. The pressor effects of angiotonin are also specifically lessened by hemorrhage (176) though epinephrine, tyramine, and isothiourea produce the usual rise of blood pressure. Using the modified Stewart method (8), Wiggers & Middleton (177) found in bled dogs that prolonged and graded hypotension reduces cardiac output and stroke volume and that reinfusion of the removed blood is followed eventually by rapid decrease in cardiac output which is the chief cause of the late decline in blood pressure (177). Still later, cardiac output may be stabilized and the low blood pressure is then related to peripheral factors, total peripheral resistance being very variable but always low before death.

The search for toxic factors in shock continues, the most definite evidence being the effect of clostridial infection in dogs when muscle tissue is made anoxic (178). Nine of thirty-two samples of such muscle exudates produced shock in recipient animals. Apparently inactive clostridia are present in the deeper cutaneous tissues of dogs but not of man as a general rule. Such infection may help explain some of the discordant results in experimental traumatic shock in animals. Also, thoracic duct lymph from animals with tourniquet shock produced a fall of blood pressure in 50 per cent of animals (179). Lymph from the burned legs of calves or dogs increases the oxygen consumption by as much as 41 per cent as compared to normal lymph (180). This activity is observed also with ultrafiltrates of lymph but less consistently with serum. A heat stable, variably dialyzable substance, which constricts the perfused vessels of the rabbit's ear (181), has been found in the circulating blood of animals with hemorrhage, traumatic shock, and burns; this substance is said to differ from histamine and the vasoactive substances produced in coagulation of blood. Chambers *et al.* (182) describe the presence in blood of vaso-excitor substances during the early period of shock and depressor substances in

the later hyporeactive period. The latter do not resemble histamine or choline derivatives.

The state of capillary permeability in regions distant from the site of injury is still an important problem meriting more direct study. Evidence of a general increase in capillary permeability is presented by Netsky & Leiter (183) who find in dogs that extensive burns of the torso and lower extremities accelerates the appearance in cervical lymph of intravenously injected horse serum. A circulatory toxic substance which increases capillary permeability generally is suggested but neurogenic factors cannot be excluded. On the other hand Cope & Moore (184) in studying the passage of radioactive colloids into lymph find no change in capillary permeability remote from the site of a burn except in one instance late in shock. In the traumatized area itself the radioactive colloids in lymph rise abruptly toward the plasma level, owing to greatly increased capillary permeability in the affected area. Fine *et al.* (185) also find no evidence of a general increase in capillary permeability even in the irreversible stages of traumatic shock in that radioactively tagged protein escapes into traumatized areas but not into untraumatized areas. According to observations on radioactively tagged red cells one-fifth of the capillary blood may be stagnant or trapped.

Using trypan blue as an indicator Lindner *et al.* (186) could not detect in lymph of shocked animals any substances which increase capillary permeability. The passage of intravenously injected fuchsin into joint fluid is increased temporarily by trauma of the same leg but not by trauma of the contralateral leg (187). The initial increase of dye passage is followed a few hours later by decreased passage and eventually by a terminal secondary increase due to anoxia shortly before death. The effects of sympathectomy on the passage of dye into joint fluids with and without trauma are described (188). It is concluded also from the disappearance curves of T-1824 that there is no general change in capillary permeability (189). Signs of severe shock do not ordinarily appear until blood volume is reduced by 15 per cent and the average blood volume reduction in severe traumatic shock is about 35 per cent (189, 195).

Concerning the reactions and responses of the minute vessels in hemorrhage and shock there is better agreement. In accord with earlier evidence it is found that the responses of the cutaneous

capillaries are affected early in hemorrhage of rats with a loss of blood only half that required to curtail mesenteric capillary circulation (190). In the rat during early hemorrhage, rhythmic constriction and dilatation of the arterioles is at first increased as is the reactivity of arterioles to chemical and mechanical stimuli. Later the flow of blood in the mesentery tends to by-pass the capillary bed, proceeding by more direct shunts from arterioles to venules (190). In man the cutaneous vessels exhibit during early shock a raised threshold for the reactive hyperemia produced by external pressure, an increased duration of reactive hyperemia, and a greater sensitivity to mechanical stimulation (191). It is suggested that these alterations of cutaneous capillary function (191), and that approximate measurements of peripheral blood flow by simplified plethysmograph (192) may be useful at the bedside in the early detection of shock in patients.

The possible role of the nervous system in the pathogenesis of shock has been reexamined. Curare (193), complete section of the cord, and section of the major nerves to a limb do not affect the development of shock following trauma to the limb, whereas procaine infiltration of the peripheral nerves and spinal anesthesia are protective, even though in the case of the latter blood pressure is lower (194, 195). Further analysis indicates that interruption of the ventrolateral areas of the spinal cord tends to prevent shock, but this effect is nullified when the ventral area is also injured. Nociceptive stimuli from traumatized regions are regarded as important contributory factors acting in conjunction with plasma or blood loss in the shock which follows trauma. On the other hand, prolonged electrical stimulation of the depressor nerves of the rabbit produces a persistent hypotension for several hours without impairing circulatory responses seriously although eventually hemodilution, anoxia, and exhaustion of the vasomotor center occur (196). Depressor reflexes evoked by stimulating the somatic nervous system are not nearly so active and the importance of a purely reflex vasodepressor reaction is questioned, though combined hemorrhage and depressor stimuli hasten death (196). Thermal injury produces an immediate rise of blood pressure, greatest in the initial burn (197) and abolished by hypophysectomy whereas like injury to a denervated foot produces a lowering of blood pressure. The rise in blood pressure is ascribed in part to

reflex responses, in part to a pressor principle the possible origins of which are discussed with emphasis on the role of the pituitary gland (197). The concentration of serum cholinesterase is reduced during shock; denervation does not prevent this change (205).

The metabolic abnormalities of severe hemorrhage and shock are outside the scope of this review but must be kept in mind because altered hemodynamics, deficient blood flow, and lowered oxygen supply can affect fundamentally the function of all tissues. Shock as it approaches the "irreversible" phase includes much more than a simple disparity between the capacity of the vascular system and the volume of blood within that system. The liver appears to be particularly susceptible and both protein and carbohydrate metabolism are involved (198 to 201). Other papers deal with abnormalities of serum phosphate (202), serum potassium (203), blood lactate (204), serum cholinesterase (205), tissue cozymase (206), tissue thiamine (207), and the inability of thiamine administration to prolong the survival times of rabbits subjected to bleeding and cold (208).

Reduced blood flow through the kidney produced by a loss of blood in unanesthetized dogs leads to the liberation of renin which is readily detectable in the circulating blood (209). Hypertensinogen decreases to very low levels in animals with kidneys but not in nephrectomized animals (209, 210). Transfusion does not increase the hypertensinogen value, presumably because of immediate change to hypertensin (209). The blood pressure response in dogs bled to the irreversible stage was not affected by renin or angiotonin (211) to which the bled animal is refractory (176); nephrectomy reduces the resistance of rats to hemorrhage (212).

The need for accurate comparison of therapeutic measures has stimulated efforts to develop dependable methods of producing shock by single massive hemorrhage (213) and by measuring bleeding volume and residual volume during fractional withdrawals at controlled rates (214, 215). It is evident also that collateral factors affect survival in shock studies. The intermittent release of a tourniquet increases both survival rate and survival time of dogs, though regional loss of fluid is equal (216). Hemorrhage reduces the required dose of pentobarbital anesthesia and hastens the rate at which anesthesia by ether is developed (217). In comparative studies on anesthetics cyclopropane appears to offer the widest

margin of safety (218, 219, 220). In ether anesthesia pretreatment with atropine is superior to that with morphine or pentobarbital (221). High protein diet (222), free voluntary movement (194, 223), and avoidance of excessive heating (224, 225) prolong survival. Objective improvement by elevating the foot of the bed is seen in mild shock but becomes progressively less as the severity of shock increases (226).

The relation of the adrenal cortex to circulatory function is summarized as part of a comprehensive review (227). Recent work indicates that adrenal cortical hormone does not modify significantly the circulatory effects of hemorrhage (228), tourniquet shock (229, 230), or burns (184, 231). In peptone shock of rats the incidence of survival is greater when massive doses of adrenal cortical extract are used, extracts of hog adrenal glands being superior to those of beef adrenals (232).

An exceptionally large number of papers deal with comparative studies on the effectiveness in shock of intravenous infusions of simple crystalloids, of blood constituents together or separately, and of substitute colloids. The effects in hemorrhage and shock of relatively large volumes of isotonic crystalloidal solutions, particularly sodium chloride, are described (173, 233 to 238) with emphasis on the benefit observed particularly if administered early and intermittently (252). In mice with hemorrhage, burns, or traumatic shock the value of large volumes of saline solution, sodium lactate, or mouse serum by mouth is said to be greater than that of serum intravenously but larger volumes are required to match the effects of whole blood or of red cells in saline (236, 237). The possible importance of dialyzable or labile, easily lost substances in blood or plasma is suggested (237, 238).

The metabolic disorders developing in late peripheral circulatory failure have prompted the addition of supplements, such as sodium succinate which seems better than glucose when added to saline (238), methylene blue which prolongs the survival period of dogs when added to plasma albumin but not when added to saline (238), and amino acids or peptides of hydrolyzed protein (239). In hemorrhagic shock, carried to the point at which reinjection of the withdrawn blood fails to produce recovery, the addition to this blood of sodium succinate, sodium lactate, sodium bicarbonate, or glucose increases the incidence of recovery (240). Best results ac-

company the use of blood with added glucose and sodium bicarbonate.

With the few exceptions mentioned above it is agreed that plasma is superior to purely crystalloidal solutions but as a balance to the overenthusiastic use of plasma alone it must be emphasized that in the circulatory failure of hemorrhage or traumatic shock it is necessary (*a*) to restore the failing circulation and (*b*) to restore the function of failing (anoxic) tissues by providing adequate oxygen transport to reverse or avoid multiple metabolic derangements. Cell-free fractions of plasma while correcting altered hemodynamics in part do not correct anemia and cardiac output remains above normal until the oxygen carrying capacity of the blood is sufficient.

Concentrated solutions of human serum albumin increase plasma volume at the rate of 600 to 900 cc. per 50 gms. of albumin injected, with an average increase of from 16 to 23 cc. per gram of albumin (241, 242, 243). Mild dehydration exerts no appreciable effect on this relation (241). There is no loss of albumin in the urine even by precipitin test and blood regeneration follows its usual course (241). Cardiac output is increased (242, 243) and peripheral resistance is diminished more with albumin than with blood or crystalloids (242). In burns the albumin concentration in blister fluid is constant at about 80 per cent of the plasma albumin while globulin concentration shows wider variation (244); this loss of protein requires in some instances very large infusions of serum or plasma protein before normal plasma volume is restored (244). In severe freezing shock of dogs neither intravenous injection of plasma nor amputation singly produces recovery but a combination of both measures is effective apparently because absorption of harmful agents is avoided while plasma volume is restored (245). In hemorrhagic hypotension in dogs intra-arterial injection of whole blood may be more effective than intravenous injection but must be done cautiously at pressures not exceeding 50 mm. Hg and at rates guided by venous pressure (246).

Gelatin infusions reduce the total circulating red cell volume in normal dogs (247) but apparently not in shocked dogs (248). Gelatin is quite rapidly lost from the circulating plasma at the rate of 50 per cent in thirty minutes, only a trace being left in seventy-two hours (247, 248). Large amounts appear in the urine (247, 248,

249). Repeated injections produce pseudo-agglutination of erythrocytes and increase the sedimentation rate without serious reactions specific to gelatin (249). Gelatin infusions, while superior to saline, are generally regarded as inferior to plasma though serviceable when plasma or blood is not available (249 to 252). Intermittent infusion of plasma or gelatin is superior to single large infusions (252, 253, 254). Pectin solutions have very limited value in dogs with hemorrhagic shock, possibly no greater than simple saline solution (255). Sudden circulatory failure suggests caution in the use of pectin (256) despite its ability to maintain effective colloid osmotic pressure and to increase blood volume in normal animals.

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RESPIRATION

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Two years ago Gemmill (76) pointed out the handicaps that beset the reviewer of the current status of problems of respiratory physiology in war-time, and concluded with the following statements:—"It may be said, however, that many advances in physiology of respiration will be made during these crucial war years. A review of these advances a few years from now will reveal this rapid progress." Both of these predictions have been amply borne out but the time has not yet arrived for fulfilling the second. Nevertheless there should be no harm in recording the opinion of the reviewer, which is that the present status of respiratory problems having more than immediate practical application to specific military situations is transitional in that the evidence now available is sufficient to invalidate conceptions previously held, or constants previously accepted, but insufficient to warrant the delineation of definitive new ones. In this the situation in the field of respiratory physiology is strikingly similar to that existing in regard to the control of the cerebral circulation (166). Both happen to have critical importance under war-time conditions because both deal with limitations to man's ability to retain military value under the stresses imposed by the conditions of modern warfare. It is for this reason that in both fields questions which previously had seemed satisfactorily settled have been reopened and the borderline between matters of remote, purely scientific value ("for the next war") and those of immediate practical importance ("for this war") has become less and less distinct until in some instances it has disappeared completely. A good example of this is found in the section immediately following.

NORMAL ARTERIAL OXYGEN SATURATION AND TENSION AND THEIR RELATION TO ALVEOLAR GASES

Until recently it was almost universally assumed [see (57) and (157) for literature] that the arterial blood of normal man, quietly breathing ambient air at sea level, is 93 to 96 per cent saturated

with oxygen. The corresponding range for pO_2 on standard dissociation curves is approximately 65 to 80 mm. Hg. Recent estimations of alveolar pO_2 collected at the end of a quiet inspiration in a large number of subjects (22, 96) gave a figure appreciably higher than the widely accepted one of 100 mm. Hg. Therefore the ΔpO_2 (difference in O_2 tension) between alveolar air and arterial blood would amount to something greater than 20 mm. Hg at rest at sea level. However, recent work has indicated that this ΔpO_2 is not a physiological factor of considerable theoretical and practical importance, as it has been thought to be, but is an experimental artifact due both to undervaluation of the arterial and overvaluation of the alveolar pO_2. The evidence is as follows.

Systematic analytical errors.—During the past five years several investigators (57, 157) have reported findings which indicate that the blood of normal subjects contains appreciable amounts of pigment of the methemoglobin type, capable of reverting more or less completely to hemoglobin during equilibration with air. Since the oxygen content is routinely determined first, before opportunity for complete reversion has been afforded, it follows that the oxygen capacity would be excessive, relative to the oxygen content and a systematic underestimation of the percentage saturation would ensue (157). Two other systematic errors also operate in the same direction, viz., more rapid drainage of cells than plasma in manipulating the blood samples, and reversion of some of the carbon monoxide hemoglobin that is likely to be present, especially in the blood of smokers (157). The apparent increase in oxygen capacity produced by these various factors is about 1 to 1.5 per cent of the total capacity for the first, about 0.8 per cent for the other two together. The sum of all three would justify raising the figure for oxygen saturation of normal arterial blood at sea level from 95 to 97 per cent. At the latter figure the pO_2 on the standard dissociation curve would be 98 mm. Hg, which practically erases the ΔpO_2 (157).

The presence of measurable amounts of methemoglobin as a normal constituent of human blood has been upheld by Paul & Kemp (145), who took samples of venous blood from one hundred hospital patients and twenty healthy blood donors and found appreciable amounts of methemoglobin (from 0.01 to 0.5 grams per cent) in all but one. Drabkin & Schmidt (57), however, were unable to find any methemoglobin (within 0.5 per cent of total pig-

ment, the limit of error of the method) in freshly drawn and promptly examined arterial blood samples from four dogs and five men. This difference may depend on an actual difference between venous and arterial blood or on the experimental procedures employed. Further work is indicated.

True arterial oxygen saturation and tension.—Drabkin & Schmidt were able to show that the arterial blood of anesthetized dogs and of normal unanesthetized men, at rest at sea level, had average oxygen saturations of 98.5 and 98.6 per cent respectively, as determined spectrophotometrically. In some of the dog experiments it was possible to make readings of the arterial blood while it was flowing through the cuvette, and here also the saturation during quiet breathing of air was 97 to 98 per cent of that seen when the animal was breathing 100 per cent oxygen. In the dog experiments the saturation was uniformly less by about 2 per cent at the end of expiration than at the end of inspiration. No corresponding fluctuations could be made out in human subjects (57). Further work is required to determine whether this is actually a species difference or is the result of the experimental procedures employed. The point has some practical as well as theoretical importance in connection with assumptions of steady states in the alveolar gases.

Direct determinations of arterial and alveolar pO_2.—Comroe & Dripps (41) have employed a special type of Scholander's micro gas analyzer (172) in conjunction with direct determinations of arterial pO_2 by the aerotonometric method. The average figure for arterial pO_2 in normal men at sea level was 97.1, the range 93 to 100.6 mm. Hg. One sample in which the arterial oxygen saturation (determined spectrophotometrically) was 99.1 per cent had a pO_2 of 98.5 mm. Hg as determined by this method (57). Comroe also collected alveolar air samples in many of his subjects and found an average figure of pO_2 97.4 mm. Hg though the individual variations were wider (86 to 104 mm. Hg) than were those for the arterial pO_2. These were samples collected at the end of a quiet expiration. Alveolar samples collected at the end of a quiet inspiration gave values that were uniformly higher (av. 103, range 99 to 112 mm. Hg). Consequently the orthodox Haldane-Priestley technic (in which the alveolar tensions are the means of these two) would give pO_2 values that are somewhat higher than arterial blood, and the procedure now in wide use of employing only the end-inspira-

tory sample would have a greater tendency in the same direction. Mackay (122) has standardized on the end-expiratory sample, but that has not been the general custom in this country.

A direct method of the type used by Comroe & Dripps has special advantages over the indirect procedure (calculating the pO_2 from the determined pH and oxygen saturation and a standard dissociation curve) when the pO_2 is higher than 50 mm. Hg, since in this range, due to the flattening of the dissociation curve, small variations in saturation mean large differences in tension. Therefore the small systematic error in estimating arterial saturation has led to more difficulty over the ΔpO_2 at or near sea level than at higher altitudes, where, because of the sharper slope of the dissociation curve, the corresponding error in pO_2 would be diminished. Thus in the blood of one subject (20) at pH 7.4 the change from 86 to 91 per cent saturation would mean an increase of pO_2 from 50 to 60 mm. Hg while at 96 per cent saturation the pO_2 would be 80 mm. Hg; the change in pO_2 corresponding with a 5 per cent change in saturation was therefore twice as great at the higher saturation. A further rise to 98 per cent saturation would bring the pO_2 to 100 mm. Hg; at this range the change in pO_2 per unit change in saturation would again be nearly doubled. The direct method is not adapted to the determination of arterial pCO_2 due to diffusion of this gas through the detergent seal in the analyzer.

Regardless of the eventual outcome of the current disagreement concerning the presence of appreciable amounts of temporarily inactive forms of hemoglobin in the arterial blood of normal man, there seems no doubt that the corresponding oxygen saturation should be raised at least to 97 and probably to 98 per cent or more. A large mass of data obtained with the oximeter is in accord with this belief (23). On the dissociation curves now in use among aviation physiologists the pO_2 corresponding with 97, 98, and 99 per cent saturation would be about 95, 105, and 115 mm. Hg respectively. In the single instance now at hand of estimations of oxygen saturation and tension on the same specimen of arterial blood by the most accurate procedures now available, the figures were 99.1 per cent and 98.5 mm. Hg (57). None of the values for arterial pO_2, as directly determined, have been higher than 100.6 mm. Hg (41). These discrepancies indicate that the dissociation curves should be redetermined with procedures that will circum-

vent the sources of error recently disclosed. The true value for arterial pO_2 is of the utmost practical importance because it is the basis for estimating the permissible amounts of other gases that will compete with oxygen, displace it, or interfere with its absorption.

THE CHEMICAL CONTROL OF RESPIRATION

The identity of the respiratory hormone.—In his painstaking and thought-provoking review in the preceding volume of this series Bernthal (17) presented reasons for the belief that the chemical factor responsible for regulating the activity of the respiratory center is the hydrion concentration within its cells and that the arguments presented in favor of a specific function by carbon dioxide are inconclusive. Banus and his collaborators (9) have recently come to the same conclusion and have advanced substantially the same reasons for it, but they have also presented some new experimental evidence in support of the acid conception and opposed to the doctrine of specific effects by carbon dioxide. They gave intravenous injections of hydrochloric or lactic acid to anesthetized dogs whose carotid and aortic reflex zones had just been denervated, and found marked decreases in alveolar pCO_2 with only minimal fluctuations in arterial pH (± 0.008 on the average). They attributed the decrease in alveolar pCO_2 to increased pulmonary ventilation and this, in turn, to the action of hydrogen ions on the center, since the chemoreceptors were denervated. A high degree of sensitivity was claimed because the changes in pH were minimal while the changes in alveolar pCO_2 were very marked.

This report deserves special commendation because, unlike most that have been presented in recent years in support of the acid hypothesis, it contains enough descriptive data to take the findings out of the class of selected case histories and to make them accessible to objective evaluation. Thanks to this it is possible to examine the basis for the authors' conclusion, and to the reviewer this basis seems very inadequate. Excluding two dogs in which anesthesia (barbital was used, with or without morphine) was unsatisfactory, there were twenty-one complete sets of observations on seven dogs. The recorded data indicated that increase in respiratory depth amounting to more than 10 per cent of the control value occurred in seven observations on four dogs; in the other

fourteen observations on three dogs the increases in depth were less than 10 per cent. Since it is expressly stated (9) that the increase in minute volume of ventilation "was mostly due to an increase in depth of respiration although in some cases the rate was also increased," it seems proper to point this out. The time elapsing between the control observations and the first samplings after acid injection, according to the stipulated procedure (injection of acid at the rate of 0.5 to 1.0 cc. per minute followed by a ten to fifteen minute pause) must have been at least thirty minutes for the smallest first dose of acid (20 cc.) and might have been as long as 115 minutes for the largest first dose (50 cc.); three of the seven instances of increased depth exceeding 10 per cent occur in this range. The other four such instances are encountered after subsequent injections of acid and therefore after considerably longer periods of time. In one of them a total of 105 cc. was injected in three periods, so that the elapsed time could not have been less than 135 and might have been as long as 255 minutes since the control period. In the reviewer's experience with dogs subjected to extensive operations under barbital anesthesia, increase in pulmonary ventilation is likely to occur spontaneously in the course of time and this may sometimes become extremely marked. In the absence of any control experiments to indicate the range of fluctuations to be expected in respiratory activity and alveolar pCO_2 in animals prepared in this manner but injected with something other than acid, there is good reason to question whether observations made over periods as long as five hours can properly be ascribed to the acid that was injected.

Apart from this, the reviewer knows of no evidence that has appeared in support of the acid hypothesis since the preceding volume of this series. Comroe (40) has recently discussed the bearing of this hypothesis on the hyperpnea of muscular exercise. The probability of specific functions by carbon dioxide in respiratory control, however, has assumed new proportions during the past year as the result of experimental work of four entirely different types. One is the demonstration by Craig (44) that addition of carbon dioxide to the oxygen overlying slices of cat cortex or medulla had distinctive effects on aerobic glycolysis and oxygen uptake; specifically, an increase from 1 to 5 per cent carbon dioxide at pH 7.4 doubled the glycolysis without increasing the oxygen consumption while the same change at pH 8.1 increased both

glycolysis and oxygen uptake by about 60 per cent. The author suggests that bicarbonate may be involved in glycolysis through an influence on pyruvate and that the results, if they have any bearing on the chemical control of respiration, may indicate that glycolysis rather than acidity is the common denominator.

A second is the publication by Gibbs and co-workers (83) of findings indicating that the addition of carbon dioxide to a mixture low in oxygen markedly increases the ability of normal men to withstand severe anoxemia. In all eight subjects mental confusion or unconsciousness and electroencephalographic (EEG) changes characteristic of cortical anoxia occurred when they breathed 8 per cent oxygen in nitrogen but mental functions and EEG returned to normal when they breathed 6 per cent oxygen plus 5 per cent carbon dioxide. Four subjects breathed 4 per cent oxygen plus 5 per cent carbon dioxide for 3 minutes without loss of consciousness and two went to 2 per cent oxygen plus 5 per cent carbon dioxide and retained consciousness for more than two minutes. Since cerebral venous oxygen saturation invariably rose and the arteriovenous oxygen difference fell when carbon dioxide was added to the inspired air the favorable result was attributed to dilatation of cerebral blood vessels. According to recent evidence (166, 170) changes in the cerebral arteriovenous oxygen difference cannot be attributed entirely to changes in cerebral blood flow but are rather an expression of a relative inadequacy or excess of the intrinsic adjustment of the cerebral circulation to the metabolic requirements of the tissue. The above interpretation may therefore be accepted with some reserve, although the alternative explanation of the decrease in cerebral arteriovenous carbon dioxide difference—a depression of cerebral metabolic activity as a result of carbon dioxide—seems unlikely in view of the concomitant improvement in mental functions and EEG. The status of carbon dioxide in the intrinsic control of the cerebral circulation is now in doubt (166, 170) and further study is indicated. At present the possible existence of a specific influence by carbon dioxide on the tone of medullary blood vessels places it tentatively in a special position as a respiratory hormone.

The third type of evidence lies in the recent reports by Ashby (6, 7, 8) of the presence of large amounts of carbonic anhydrase in various parts of the central nervous system. The content of enzyme in the brain was relatively constant (7.4 to 14 per cent of

that in the blood) in different species (6), was about twice as high in the brain as in the cord (7), and the distribution in different parts of the central nervous system was strikingly parallel to the recorded values for the oxygen consumption of the same portions (7). A possible relation of this enzyme to the chemical reactions underlying the functions of these tissues is suggested (6, 7).

The fourth is the recent discovery of a specific enzyme system by which carbon dioxide can be fixed in animal tissues (63, 64, 120). This process is supposed to be responsible for the conversion of pyruvate to oxaloacetate and it may therefore be implicated in the tricarboxylic (citric) acid cycle of carbohydrate oxidation (63). So far these transformations have not been demonstrated in brain tissue but the fact of their existence deserves mention in this connection.

None of these items is at present in a state of sufficient development to warrant categorical statements as to its immediate or probable significance to the question of the specificity of carbon dioxide as a respiratory hormone. Yet the mere possibilities that there may exist in the cells of the respiratory center specific enzyme systems by which carbon dioxide can enter into energy-yielding reactions, either by direct fixation in carboxyl form or after transformation into bicarbonate, and that the gas may preside in a special manner over the blood supply of the brain, seem to the reviewer to introduce into discussions of the identity of the respiratory hormone a type of reasoning that could not have been foreseen when either of the current conceptions was formulated. It may still be possible that carbon dioxide affects respiration solely by reason of the hydrogen ions that are split off from the carbonic acid formed when it dissolves in water, but the unquestioned fact that respiration is stimulated much more powerfully by carbon dioxide than by any other acid-forming substance (given the same change in arterial pH in both cases) still remains to be satisfactorily explained on this basis. In the reviewer's opinion, the recent developments cited above have greatly increased the probability of specific effects by carbon dioxide and have correspondingly weakened those of the hydrogen ion's being the all-important agency.

The opposing opinion of Bernthal (17) starts with the basic assumption that the intracellular acid hypothesis is an established fact. He points out that the true state of affairs inside the respiratory center then is not necessarily revealed by examination of the

arterial blood, that absence of stimulation by acid injected directly into the respiratory center of animals does not necessarily disprove its sensitivity to acid, and that failure of hyperpnea to occur in man when acidosis is produced by ingestion of ammonium chloride may be referred to unequal rates of diffusion of the two ions of the salt or to a direct depressant action by one of them. Banus *et al.* (9) present substantially the same arguments though with less emphasis on the first and more on the other two. None of these claims can be refuted. However, if they are separated from the assumption that the acid hypothesis has been established beyond question and that the burden of proof must necessarily be on those who hold otherwise, they seem to the reviewer to hold implications that deserve comment. If neither the analysis of arterial blood nor direct injections of chemical substances into the respiratory center can be used to examine the validity of the intracellular acid hypothesis the latter has passed beyond the range of experimental proof as well as disproof. The only type of supporting evidence then is the occurrence of respiratory reactions that cannot be attributed to changes in the chemical composition of the blood. As pointed out elsewhere (40, 42), the intracellular acid conception was one of several propositions intended to explain discrepancies such as these, but the necessity for all of them has largely disappeared because of the subsequent discovery of reflex factors capable of accounting for most or all of the previously unexplained discrepancies (40, 42, 164, 169). Therefore it does not seem profitable any longer to stress evidence of this type in support of the acid hypothesis. In any case there is no evident reason why this general conception should be restricted to the hydrogen ion, for if direct proof is not demanded the choice of stimulant agent assumed to be involved is a matter of individual preference, so long as it is a product of cellular metabolism. Finally, if failure of the ammonium chloride experiment to agree with expectations is to be attributed to properties peculiar to this particular acidifying substance it is obligatory to examine every other chemical stimulant agent for corresponding specific features and no basis will remain for belief in any common denominator for chemical stimulation, regardless of its location with respect to the cells of the center. As far as ammonium chloride is concerned, the argument is not particularly strong because the acidifying effect is generally believed (147) to be due to prompt conversion of the NH_4 radical to urea, for which

no specific respiratory functions have yet been claimed. With respect to unequal rates of diffusion of the two ions into the center (17), these could scarcely have been important in the experiments under criticism because they lasted as long as ten days; this has already been emphasized repeatedly (161, 168) and no reason has been advanced to change that opinion.

In the opinion of this reviewer, the reasons for believing that carbon dioxide exerts specific effects in respiratory control (i.e. that its actions cannot be ascribed entirely to hydrogen ions formed from it) seem to have been considerably strengthened by these recent developments. The subject obviously is in a transitional stage but it is to be hoped that further work along the lines noted above will eventually afford a rational biochemical basis for the superiority of carbon dioxide over other acid-forming agencies in stimulating breathing, as well as for the stimulant effects of bicarbonate (but not of carbon dioxide) when injected directly into the center (40). Bernthal (17) has presented some plausible reasons for the latter phenomenon; a species difference (e.g., lack of adequate carbonic anhydrase in this region in the cat) may also be involved.

Acetylcholine and respiratory control.—The background of Gesell's recent proposal that acid plays an important role in decreasing the activity of cholinesterase, thereby augmenting the transmitter effects of acetylcholine, has been fully presented in the preceding volume of this series (17). Like all of Gesell's conceptions it is ingenious, plausible and—granted certain basic assumptions—very satisfying. In this particular case the assumptions are that acetylcholine plays an important part in the functioning of the respiratory center, and that—if it does—the changes in pH that might be expected to occur in the center under physiological conditions could, through altering the activity of cholinesterase within its cells, bring about significant changes in the cellular activities related to acetylcholine. The evidence bearing on these two assumptions up to a year ago was reviewed in the preceding volume (17) and will not be discussed here with the exception of one paper (79) which, since it is now being referred to as proof that acetylcholine actually is concerned in respiratory control, calls for brief comment. In the present reviewer's opinion practically all of the observations there reported can be attributed to asphyxia resulting from spasm of bronchial muscle (due to physostigmine), fall in

blood pressure (produced by acetylcholine), removal of the peripheral muscarinic actions of both drugs (by atropine), or direct depression of the central nervous system (by large doses of atropine into the vertebral artery). The first of these certainly was not eliminated by the measures taken to exclude it (constant artificial respiration and bilateral pneumothorax), for substantially the same procedure is the basis for one of the standard methods [that of Jackson (106)] of demonstrating the actions of these and other drugs on the bronchial musculature. The cardiovascular effects of these drugs were not mentioned but some of them must have been quite marked. The actions of atropine on the central nervous system are not well understood but it is certain that large doses given via the vertebral artery can cause severe depression (160).

Gesell believes that the actions of acetylcholine on the central nervous system are not nicotinic (atropine-resistant) but muscarinic (atropine-sensitive), and during the past year two papers have appeared which support this belief. Calma & Wright (29) state that 1 mg. of atropine can annul the central nervous effects of a previously effective dose of acetylcholine. (The record submitted in evidence shows a quite normal response as long as five minutes after the intravenous injection of atropine, the described abolition at eight minutes, and beginning of return at fifteen minutes, which means a remarkably long latent period and brief duration for the characteristic actions of atropine, but the reviewer has no explanation to offer.) They also point out that physostigmine undoubtedly has direct effects on the central nervous system but that these are unpredictable, show wide species and individual variations, and are subject to great modifications by the anesthetic, preparation, and other accidental influences. Luco & Altamirano (121) found that atropine was able to exert a curare-like influence on neuromuscular (superior rectus) actions and curare an atropine-like influence on the muscarinic (submaxillary gland) effects of acetylcholine in the cat. The dose of each varied directly with the threshold of the tissue for acetylcholine: if the latter is high (as is the muscle) the required dosage of atropine will be large and that of curare will be small, while if it is low (as in the salivary gland) the reverse will be true. Miller (135) found that atropine (4 mg.) abolished or prevented the previously marked effects of local applications of acetylcholine to the hypoglossal nucleus in decerebrate cats. These effects (furrowing of the tongue, elevation of the

palate, acceleration of respiration) were attributed to diffusion of acetylcholine into the subjacent synapses and the specificity of the action is said to be established by the influence of atropine upon it. In this case, however, systemic effects by acetylcholine seem to have been a strong probability.

These recent papers, in the reviewer's opinion, add to the suspicion, already quite widely held by pharmacologists, that the actions of atropine (or of any other drug, for that matter) on the central (or peripheral) nervous system are incompletely understood, but they do not warrant the conclusion that the drug can antagonize the actions of acetylcholine on this system in the same sense that it overcomes the peripheral muscarinic actions of the latter. That atropine does not noticeably block the spread of cholinergic excitations to the respiratory center can easily be demonstrated by the administration of acetylcholine after atropine: the characteristic hyperpnea (originating in the chemoreceptors) is not prevented by large doses of atropine. As far as physostigmine is concerned, the indications are that its actions are by no means confined to inactivation of cholinesterase—a fact that has already been known for some time (124). In the reviewer's opinion, the use of these drugs as physiological reagents to elucidate problems of the integration of respiratory control (or of other nerve functions) should await more definite information about the details of their actions than is now available. No drug has yet been discovered that has only one action when it is distributed throughout the body in effective dosage, and the burden of proof is on anybody who claims complete understanding of the actions of any potent drug.

Gesell and his collaborators have also reported studies of the effects of acid on the response of the turtle heart (80) and rectus abdominis muscle of the frog (67, 81) to acetylcholine. The results were in accord with expectations: the response was increased by acid, and the curve obtained by plotting the reciprocal of the height of contraction against the pH was said (81) to be roughly comparable with that given by Glick (87) for hydrolysis of acetylcholine by cholinesterase *in vitro*. No observations were made with atropine, physostigmine, choline, or its stable derivatives to permit evaluation of the part played by altered activity of the cholinesterase system, nor were the possible effects of pH on functions other than cholinesterase excluded. Andrus (5) found that choline as well as

acetylcholine had greater inhibitory effects on rabbit auricle at pH 7 than at pH 8, which is strong evidence that something other than delayed hydrolysis of acetylcholine must have been concerned because choline is not inactivated by cholinesterase.

The evidence thus far presented is not sufficient, in the reviewer's opinion, to substantiate either of the assumptions that underlie this conception (p. 240). Even if it were, developments of the past few years have indicated that the situation with respect to the functions of acetylcholine in the nervous system is vastly more complicated than it was previously thought to be and judgment as to the significance of sensitivity of the cholinesterase system to acid certainly should be withheld until more is known about its relation to other factors now believed to be concerned. The role of acetylcholine as a transmitter of excitations in central and peripheral nerve tissues is under intensive study, as a glance at current volumes of the *Journal of Physiology*, the *Journal of Neurophysiology*, *Helvetica Physiologica et Pharmacologica Acta*, *Pflüger's Archiv*, and the *Index Medicus* will disclose. The present trend of these studies is to link the cholinergic system with the intracellular biochemical processes involved in glycolysis, phosphorus metabolism, cationic equilibria, and vitamin functions, but the various inter-relations that are now supposed to exist are so complicated that the present reviewer finds them utterly bewildering.

The acetylcholine cycle.—Two suggestive schemata have recently been published (138, 159) and the interested reader is referred to the original publications for details. Both agree that the biological synthesis of acetylcholine depends upon energy derived from glycolysis. According to Nachmansohn (137), the place of acetylcholine in the cell economy would rest upon the rapidity with which its stored-up energy can be liberated on hydrolysis by cholinesterase. Compared with oxidation, some 5,000 to 10,000 times as many molecules of acetylcholine could be split, per unit of tissue and time, as the number of oxygen molecules that could be taken up (137). Therefore release of acetylcholine becomes most important in systems characterized by brief spurts of intense activity, such as the electric organ of the electric eel (137, 138) or the nerve fiber (139). The fact that the cholinesterase content of the sheath of nerve is much higher than that of the axis cylinder while the content of oxidative enzymes shows the reverse relationship (140, 141) is in accord with this conception. Since phosphate bonds

are the most readily available sources for storing energy in easily available form it is reasonable to suppose that labile phosphorus compounds are involved in the resynthesis of acetylcholine, and experimental evidence in support of this has recently been advanced (58, 138). According to both of these authors, conversion of adenosinetriphosphate to adenosinediphosphate is capable of liberating more than enough energy for the synthesis of acetylcholine from its constituents; one points out that this is the only known biological agency that can react with both glycolytic and respiratory systems and capture energy from both of them (58). This may explain the reduction in cerebral acetylcholine content produced either by anoxemia or glycolysis (198) and the fairly close parallelisms among age, acetylcholine content, oxygen uptake, glucose utilization, and glycogen storage in different parts of the neuraxis (200).

But, according to a recent study (58), the enzyme system involved in the adenosinephosphate transformations is highly sensitive to changes in the amount of available calcium, and the suggestion is made that perhaps liberation of free calcium may be the first step in the activation of the triphosphate-diphosphate change. One then thinks of the increase in neuromuscular excitability (and in sensitivity to acetylcholine) associated with calcium deficiency, the decrease or block in transmission associated with calcium excess (115). Since calcium is frequently counterbalanced by potassium in living systems it becomes possible that some of the effects of potassium on nerve functions may enter the picture at this point. Recent work (111) has shown again that the synthesis of acetylcholine in both the central and peripheral nervous systems is increased by the addition of potassium. Finally dicarboxylic and tricarboxylic acids have recently been found (58, 139) greatly to accelerate the rate of formation of acetylcholine in nerve tissue, and the suggestion is made that glutamic acid, citric acid, or both may act as coenzyme in the biological synthesis of the ester (139). Apart from the direct relationship thus suggested with the citric acid cycle of carbohydrate breakdown (63), the ability of citric acid to inactivate calcium gives rise to a new set of possibilities here.

Carbohydrate metabolism is also thought to be implicated in the provision of the acetate radical required for combination with the choline liberated [doubtless by a still unknown enzyme, perhaps as phosphoryl choline (138)] from the phospholipids of nerve

tissue. It is supposed (159) that the acetyl radical is derived from pyruvate or acetate and that in the absence of glucose oxidation no other aerobic source is available. This is borne out by experimental data (159) indicating that acetylcholine formation in the brain increases (and decreases) with the glucose concentration and also with the changes in oxygen uptake produced by cyanide.

Finally, several recent publications point to an intimate relation between these reactions and thiamine (aneurine, vitamin B_1). Nachmansohn *et al.* (140) found that the concentration of diphosphothiamine (cocarboxylase) in the sheath of nerve was several times as high as that in the axis cylinder, and noted that since this distribution resembled that of cholinesterase more than it did that of oxidative enzymes it would support the assumption that thiamine is required for the formation of acetate from pyruvate preliminary to the formation of acetylcholine, Subsequently (141) he found that the amounts of pyruvic dehydrogenase also were greater in the sheath than in the axis cylinder, and that the activity of this enzyme was greatly increased by the addition of diphosphothiamine. Von Muralt and his associates (118, 192, 203) have presented experimental evidence which indicates that thiamine is liberated from peripheral nerves on stimulation, that it too is present in much greater amounts in the sheath than in the axone, and that the amounts liberated on stimulation are approximately twenty times as great as those of acetylcholine. Like acetylcholine, thiamine is supposed to exist in two forms, bound and free (203). There appears to be general agreement that thiamine is concerned in the formation of acetate from pyruvate. It is suggested (118) that thiamine is involved in either the aerobic or anaerobic transformation of pyruvate to acetate, as follows:—

$$\text{Aerobically, } 2\ CH_3\cdot CO\cdot COOH + O_2 \rightarrow 2\ CH_3\cdot COOH + 2\ CO_2$$

$$\text{Anaerobically, } 2\ CH_3\cdot CO\cdot COOH + H_2O \rightarrow CH_3\cdot COOH + CH_3CHOH\cdot COOH + CO_2$$

The finding of Smith *et al.* (178) that thiamine-deficient cats showed a heightened resistance to anoxia probably has no bearing on this matter because, as the authors were careful to point out, the same effect was produced by starvation and was probably nonspecific for thiamine. Vitamin C is also said to be involved in the acetylcholine cycle (70).

In view of these fragmentary glimpses of complex interrelation-

ships that were entirely unsuspected a few years ago, it seems to this reviewer that no useful purpose can now be served by picking out one single, simple physicochemical relationship (the influence of acids on the hydrolysis of acetylcholine by cholinesterase *in vitro*) to serve as the basis for a conception of the integration of nerve cell functions in the whole organism. Previous ideas about the characteristics even of the simplest possible form of this system (the effect of acid on the hydrolysis of pure acetylcholine by cholinesterase *in vitro*) have been brought into question by the recent work of Mendel *et al.* (132, 133, 134), who have isolated two types of the enzyme (true and pseudo) and have found quite marked differences in the manner in which the action of the two forms on acetylcholine is affected by various factors. They did not study the influence of acid on the purified true esterase obtained from brain; until this is done, the bearing of data, obtained *in vitro* with less purified preparations (87, 138), on the properties of the esterase system *in vivo* must be viewed with suspicion.

Apart from this, it would be quite remarkable if of all the various enzyme systems that enter into the acetylcholine cycle as it is now envisaged, only one (that which hydrolyzes acetylcholine after it is formed) should be sensitive to acid. The reviewer is unfamiliar with data bearing on studies along these lines under conditions approaching the physiological. According to one recent report (21) the stability of thiamine toward thermal decomposition is markedly influenced by pH changes in the same manner, but to a considerably greater extent than the hydrolysis of acetylcholine by cholinesterase at body temperature. Thus the rate of destruction of thiamine in boiling phosphate buffers was maximal (90 per cent) at pH 7.4, and 48 per cent at pH 7.0 (21), while the hydrolysis of acetylcholine by cholinesterase was maximal at pH 8.5, 70 per cent of this at pH 7.5, and 55 per cent at pH 7.0 (87). The thermal destruction of cocarboxylase was much more sensitive to acid than was that of thiamine (21). The applicability of these findings based on thermal destruction to possible effects of acid on enzyme equilibria *in vivo* is of course open to question, but the fact that they exist and that a biologically important combination of thiamine (cocarboxylase) is much more labile, at least suggests that sensitivity to acid is not a peculiar prerogative of cholinesterase. If it is true that the amounts of thiamine involved in impulse transmission are twenty times those of acetylcholine (192), the

possible sensitivity of the thiamine part of the cycle to acid can scarcely be ignored. As for the other parts of the cycle, it is not unlikely that the influence of acid will be found to vary considerably in direction as well as degree. Perhaps considerable cancellation occurs in this respect, possibly even to the extent of complete equality of effects in opposite directions, in which case the final activity of the complete acetylcholine system *in vivo* might be completely unaltered by acid although some of its component parts can be shown to be sensitive when treated as isolated entities. Obviously such speculations serve only to emphasize the desirability of withholding judgment, pending further experimental evidence, as to the probable physiological significance of the sensitivity of the cholinesterase-acetylcholine system to acid *in vitro*.

Anoxia

Large numbers of observations have been and are being made in conjunction with the indoctrination and training of flight personnel as well as research activities related to aviation, but the results, with few exceptions, are not yet available. A few studies (12, 30, 93, 129, 193, 206) that may be regarded as representative have appeared in the past year and one of them (193) presents an excellent account, not only of the historical background of aviation physiology but also of the difficulties involved in the selection and use of suitable test procedures. It is of special importance because it contains a detailed survey of recent German literature which has not been available in this country. As far as one can tell from the author's account, American physiologists have completely closed the gap which previously existed between them and the Germans, but there is of course no means of knowing about material not yet published. The more clinical aspects of anoxia are taken up by Comroe & Dripps in the chapter on Applied Physiology and those pertaining to chemoreceptor functions are considered below. At this point a number of recent papers dealing with some of the fundamental effects of anoxia will be summarized.

The ceiling for survival.—The lowest ambient pressure at which rats could survive in an atmosphere of 100 per cent oxygen averaged about 60 to 65 mm. Hg (91); this corresponds with an altitude range of about fifty-six to fifty-eight thousand feet. If an alveolar pO_2 of 10 mm. Hg is taken as the critical level for survival it follows that the sum of pCO_2 and pH_2O could not have been more

than 50 to 55 mm. Hg and in the most resistant animal (which survived at 50 mm. Hg) it was only 40 (91). Since the accepted values for alveolar pCO_2 and pH_2O at sea level are about 40 and 47 mm. Hg respectively, it is obvious that considerable reduction in one or both of these must have occurred. Possible mechanisms for diminution in alveolar pH_2O are mentioned (91). Stullken (184) found average ceilings (mm. Hg) of 70.7 in oxygen and 158.6 in air for mice, 89.5 and 218.3 for chicks, and attributed the superior tolerance of mice to their rapid breathing. The altitude equivalents for mice are 54,500 and 37,500 feet respectively.

Relation of age to resistance to anoxia.—This has been studied in several ways, the results agreeing in indicating a markedly greater resistance in newborn animals. Selle (176, 177) extended his earlier studies on the type and duration of gasps by the decapitated head of the rat and found the movements to last 25 to 30 minutes in the case of newborn animals, whereas at subsequent periods the duration was progressively shorter, viz. 12 to 16 minutes at seven days, 4 to 7 minutes at fourteen days, 2 to 3 minutes at twenty-one days, about 1 to 2 minutes at twenty-eight days, and none after five to six weeks. Glass *et al.* (86) exposed rabbits, dogs, and guinea pigs to pure (99.9 per cent) nitrogen at sea level and found the first two to survive for markedly longer times when newborn than at any subsequent time; in rabbits the survival times were newborn 34 minutes and adult (eighteen days after birth) 1½ minutes, while in dogs the corresponding figures were 31 and 3 minutes (reached four weeks after birth). Rabbit fetuses delivered by hysterotomy at the onset of viability (twenty-nine days out of a thirty-two day gestation period) survived 44 minutes and at thirty days, 41 minutes, but rabbits delivered after gestation had been artificially prolonged to thirty-five days showed the same survival time (about 16 minutes) as rabbits three days after birth at term. Thus the high resistance of newborn animals appears to be due to their imperfect state of development and not to their environment —a conception that is borne out by the fact that guinea pigs, which are born in a much more mature state than rabbits or dogs, showed only insignificant differences in survival time between the newborn and adult states (4½ and 3 minutes respectively).

A change in type of energy metabolism of the brain (of the rat) corresponding with these findings has recently been reported (34). The curve of aerobic activity started from a low level at birth, rose

rapidly thereafter to a peak at four to eight weeks and then fell off. Glycolysis behaved similarly. The anaerobic curve was very close to the aerobic at birth but then rapidly fell; the "anaerobic deficit" (the difference between the caloric production in an atmosphere of carbon dioxide-nitrogen and in carbon dioxide-oxygen) therefore was very low at birth but rapidly increased afterward. There were only minor differences between the cortex and the brain stem in these respects, but it is interesting that up to five days the brain stem had a higher energy metabolism than the cortex while at the fiftieth day the relation was reversed. The supreme importance of glycolytic processes to survival of adult animals (dogs and cats) breathing mixtures low in oxygen was deduced from the observation (65) that the survival time was greatly shortened (average figures 151 and 4.3 minutes) by the administration of monoiodoacetic acid. While the conclusion is reasonable the value of the evidence is greatly diminished by the fact that the monoiodoacetic acid apparently depressed the circulation markedly (as indicated by an increase in the cerebral arteriovenous oxygen difference) and killed all of the air breathing controls although it did not prevent rises in the lactic acid content of blood and brain during anoxia.

The influence of temperature.—The effects of rapidly lowering body temperature were studied in anesthetized dogs by means of the Rein devices for measuring blood pressure, leg blood flow, and alveolar oxygen and carbon dioxide (90). Respiration and circulation were first stimulated, the effect reaching its peak at a brain temperature of 34.5° C. At a temperature of 26° C. depression had replaced stimulation and at 22 to 20° C. failure of respiration occurred.

The ability of cold to reduce the damaging effects of anoxia on the central nervous system was demonstrated in several ways. The spinal cord of the cat survived much longer periods of acute anemia (produced by injections of Ringer's fluid under high pressure into a previously prepared pocket) when the animal was cooled to about 27° C. than when it was at 38° C. (188). Studies of the oxygen uptake by the cord substantiated this conclusion. Slices of rat brain and kidney were not damaged by exposure to 0.2° C. for periods as long as one hour, for their oxygen uptake came back practically to the control level on subsequent warming (71). The lethal effects of severe cold therefore are more likely to be due to

failure of the "supply mechanisms" (respiration and circulation) than to direct damage of the brain (71). Further studies along these lines (72) indicated that while immediate chilling led to the preservation of a higher subsequent oxygen uptake in the case of liver and kidney, there was no difference in the case of the brain. This is taken to mean that the brain, since it lacks the ample carbohydrate stores available to the other tissues, undergoes irreparable damage before its metabolic processes can be arrested by the cold. In confirmation of this it was found (66) that brain slices exposed to temperatures higher than 40° C. showed a progressive decline in oxygen uptake although the oxygen supply was otherwise ample. Complete recovery could occur after three hours at 40° C. but not after thirty minutes at 40.8° C. It is pointed out that the brain can stand greater and longer excursions below the normal body temperature than above it, which is worth emphasizing in connection with the growing popularity of fever therapy. There was a thermostable oxygen uptake amounting to about 10 per cent of that at 37.5° C., which is about the same fraction that remains after chemical inhibitors have been applied; the authors suggest that it may be the same biological process. The conception that acute anoxia can be produced in the brain by increasing its activity in the presence of an otherwise adequate oxygen supply is borne out by recent experiments with drugs (see page 252 below).

Other studies bearing on the ability of animals to withstand severe anoxia were made by Oster *et al.* (144) and by Craig & Beecher (16, 44, 46). The former exposed intact adult cats to mixtures low in oxygen and found that subsequent complete recovery occurred regularly if artificial respiration with air was begun as soon as spontaneous breathing had ceased. The range of oxygen content studied was from 0 to 5 per cent; 3 per cent appears to have been a critical level, since the average survival time at zero oxygen was 2.2 minutes and at 2.4 per cent it was 3.4 minutes, whereas at 3 to 3.19 per cent it had risen to 20.1 minutes. The altitude equivalents of 2.4 and 3.1 per cent oxygen are approximately 50,000 and 45,000 feet. Eichler *et al.* (60) report a tremendous though transitory increase in the histamine content of blood plasma in cats breathing 10 per cent oxygen (equivalent to 18,000 feet); the curve showed a rise from a normal of 0.056 to 0.12 to levels as high as 480 μg. per cc. in the first ten minutes, maintenance of the high level for about thirty minutes, and return toward

or to normal within an hour. The probable significance of this is unknown to the reviewer, to whom only an abstract of the paper has been available.

Craig & Beecher (46) studied the influence of changes in oxygen tension on the oxygen uptake and glycolysis by slices of different parts of the neuraxis of the cat. Important findings included a gradient in both functions (cortex: medulla: cord = 100:34:12 for oxygen uptake in 100 per cent oxygen, 100:17:5 for anaerobic glycolysis, the latter showing a maximum in the medulla at 2 to 3 per cent oxygen), and a direct variation of oxygen uptake with the oxygen tension of the environment. Thus the Q_{O_2} under 100 per cent oxygen and room air were, for cortex, 10.5 and 7.1, for medulla 3.5 and 2.3, and for cord 1.3 and 1.0. This may be entirely dependent on diffusion of oxygen into the slices; if not, a relation to oxygen toxicity is suggested (46). The same workers (16) studied the same functions in brain cortex, kidney cortex, heart muscle, and liver of cats subjected to hemorrhage large enough to keep the blood pressure at or below 70 mm. Hg for one to four hours; ether anesthesia was used and the body temperature was allowed to fall. The observations indicated that the functions studied were not significantly different in the shocked animals as compared with unbled controls; the Q_{O_2} for brain cortex was about 11 in the controls, 12 in animals given ether only, and 12 in the bled series. These *in vitro* values are strikingly similar to the normal mean Q_{O_2} recently reported for the monkey's brain *in vivo*, viz. 11.1 (170), but this is for the whole brain, not for cortex alone. Since the Q_{O_2} of the white matter is probably no more than half that of the cortex, the *in vivo* value for cortex alone should have been considerably higher than this (170). Beecher & Craig (16) were careful to state that the conclusion that cerebral metabolism is not measurably altered in hemorrhagic shock is subject to the reservation that the statement applies only to the portion of the metabolism that persists *in vitro*. The conclusion that anoxic changes in the brain are not an important factor in the course of hemorrhagic shock is supported by the failure of oxygen inhalation to alter the outcome (69). The underlying question is one of considerable importance but, like all related to anoxia, it is fraught with so many variables that a categorical answer is impossible at present. In the reviewer's opinion, the studies mentioned above (16, 66, 170) justify the suspicion that among the mechanisms involved in the

utilization of oxygen by the brain there are highly labile, moderately stable, and very rugged moieties and that the *in vitro* technic deals only with the latter two. Further work along these lines is desirable.

The work of Craig (44) dealing with the influence of carbon dioxide on the oxygen and glucose metabolism of the brain and medulla of the cat has already been mentioned (p. 236). Anoxia (3 per cent oxygen) was found to increase the lactic acid production in cortex markedly (by 114 mg. per gram of tissue), that in the medulla only slightly (by 8 mg. per gram). This points to the operation of factors that are at present not understood and bespeaks caution in drawing conclusions as to acidity within medullary cells (such as the respiratory center) from observations made on other parts of the brain during anoxia.

The influence of drugs etc. on the tolerance to anoxia.—Stimulation of metabolism by thyroxin or dinitrophenol decreased the resistance of rats to decompression, and thiourea administration or thyroidectomy increased it (116). This is in accord with the effects of temperature noted above. Duration of survival of the decapitated rat head was found to be prolonged by glucose feeding and by substances that raise the blood sugar (epinephrine, anterior and posterior pituitary extracts), shortened by insulin and monoiodoacetic acid (98, 176, 177). Desoxycorticosterone administration decreased the tolerance of rats to decompression in spite of the fact that adrenal cortical lipid is decreased; the unfavorable result is attributed to cardiac lesions produced by the administered sterol (49). Cobalt feeding produced its characteristic polycythemia in rats but their performance at 6.8 per cent oxygen (equivalent to about 28,500 feet) was not strikingly improved until the cobalt feeding was discontinued; performance then rose to about double its base level (56). These findings are attributed to two opposing effects by cobalt, one (polycythemia) favoring performance, the other (presumably a direct toxic action) impeding it (56). According to another criterion polycythemia induced by transfusion of erythrocytes in saline did not have any beneficial effect on the altitude tolerance of rats (201). A high carrot diet was found to increase quite markedly the ability of rats to survive at high altitude although it did not alter the EEG response (109), but no corresponding effect was evident when the criterion was a different one (201). Emerson & van Liere have developed a standardized technique

for studying the influence of drugs on anoxia tolerance in mice (62) and have reported some beneficial effects from certain sympathicolytic and parasympathomimetic agents (dioxane derivatives, ergotamine, betaine, prostigmine) but choline derivatives and physostigmine had no similar action and sympathomimetic compounds (ephedrine, amphetamine, propadrine, mescaline, hordenine) were either useless or harmful (62). A combination of prostigmine and dilantin (to prevent the convulsions which either anoxia or prostigmine causes in mice) gave good protection but the required dosage was not far below the lethal range (61). Hoff & Hoff & Yahn (103) found that dilantin alone caused a distinct imimprovement in the altitude tolerance of rats and mice, perhaps because of its anticonvulsant action, perhaps because of a decrease in basal metabolic rate.

An approach to some more fundamental aspects of the relation of drug actions to anoxia is one of the outstanding developments of the past year. McCulloch and his co-workers (52) reported that the pO_2 in the cortex of the cat (measured by an open oxygen electrode) showed a marked fall associated with convulsions produced electrically or by means of drugs; this fall began before the first clinical or EEG manifestations of convulsions and was maximal about one half minute after the seizure. In the absence of calibrations in terms of actual oxygen tensions these results must be accepted with some reserve, though the general conclusion—that convulsant agencies give rise to a marked increase in cerebral metabolic activity—is unquestionably sound. Davies & Brink (51), using a closed type of oxygen electrode and checking their readings against *in vivo* calibrations, have found that the pO_2 in the resting (anesthetized) cortex of the cat may vary from practically arterial to nearly zero, depending on the position of the electrode in relation to major blood vessels. Abreau & Woodbury (1) concluded that asphyxia is the cause of death in strychnine convulsions (in dogs), not fatigue of the centers, while Dragstedt *et al.* (197) presented evidence to indicate that picrotoxin causes a marked and prolonged increase in the excitability of the respiratory center to electrical stimuli. Work on monkeys in this laboratory (170) has shown that cerebral oxygen uptake varies directly with the degree of cerebral activity, that the "physiological" range (i.e., that compatible with complete reversibility) is from about half to nearly double the resting cerebral oxygen uptake, the high value being

produced by convulsant drugs, and that following an increase of this order a prolonged and marked decrease ensues. The last-named observation confirms an earlier one (160) made with less accurate orientation as to actual cerebral metabolism in indicating that cerebral anoxia, with all its consequences, can be produced quite as well by increasing the oxygen uptake by the brain beyond the capacity of the existing oxygen supply, as by decreasing the oxygen supply below the existing oxygen demand. The implications of this conclusion with regard to the therapy of certain types of cerebral anoxia are discussed elsewhere (170). The effects of anemia of the brain (74) and spinal cord (186, 187, 188) have been studied.

Descriptions of anoxic phenomena in man are given by von Tavel (193) and by Ward & Olson (194). The latter report is of particular interest because it indicates that severe anoxia may cause a marked hyperthermia, a factor to be considered in connection with direct stimulant effects by anoxia on the respiratory center (see below).

The cerebrospinal pressure of dogs was found not to be significantly raised by quite severe anoxemia (7 to 10 per cent oxygen) over a period of an hour or more (15). Swelling of the brain must be moderate if it occurs at all (15).

Hyperventilation

The clinical syndrome of hyperventilation as it is encountered in civilian practice has been discussed in several recent papers (31, 142, 143, 153). Its importance in aviation was also considered (100). The human EEG characteristically showed a marked diminution in frequency and increase in amplitude, the change being most marked in subjects with abnormal cortical activity to begin with (82, 153) and associated with an increase in heart rate (48). The "self-sustained" cortical activity in cats, i.e., that following direct electrical stimulation, was diminished by hyperventilation (53). A classification of clinical states associated with hyperventilation is given by O'Donovan (142). The manner in which cerebral functions are affected by hypocapnia has not been elucidated. Dizziness, blurred vision, muscular cramps, vasomotor collapse and unconsciousness may occur and these are ascribed to interference with the dissociation of oxygen from hemoglobin (100). Constriction of cerebral blood vessels (82) and fall in blood pressure (143) have also been implicated. The development of a method for measuring

cerebral blood flow in man (110) makes possible the investigation of these questions, which at present are quite unsettled (166, 170). The recent trend of thought in regard to the possible involvement of calcium ions in the acetylcholine cycle (p. 244) and of the special importance of pCO_2 and bicarbonate in the control of nerve cell function (p. 236) introduces an entirely new set of possibilities here.

RESPIRATORY REFLEXES

Carotid and Aortic Bodies

The part played by reflexes from these structures in the control of breathing has been discussed in a series of publications from this laboratory (40, 42, 161, 164, 167, 168, 169) and the following views were held to be in best accord with the available evidence: The hyperpnea of anoxemia is mainly if not exclusively due to chemoreceptor reflexes; in its effects directly on the center anoxia is essentially depressant (161, 164, 167, 168). The hyperpnea of acidosis may be due in part to an action on the center (either through a change in pCO_2 or by the hydrogen ions themselves) but the chemoreceptors can be involved if the change in arterial pH is sufficiently marked and perhaps (though this remains to be proved) these are the only parts of the respiratory regulating system that are directly sensitive to hydrogen ions (161, 163, 168). The hyperpnea of hypercapnia can involve both direct stimulation of the center and reflexes from the chemoreceptors, but the central response is definitely the more sensitive and produces the more marked effects (161, 164, 167, 168). Changes in blood temperature may also affect respiration in part through these reflexes (161, 167).[1] Tonic activity of some of these organs during quiet breathing at sea level is demonstrable in laboratory

[1] To make the record clear it appears desirable to point out that in the experiments made in this laboratory on the effects of temperature on the carotid chemoreceptors (as in all others of this type) utmost pains were taken to insure that the perfusion fluid did not enter the systemic circulation. Definite statements to that effect unfortunately were omitted from the preliminary report and subsequent discussion (161) of the findings and the further work that was to have been the basis for a more complete presentation was prevented by the unexpected course of events. It is beyond belief that any worker with experience in this field would be so careless as to perform, or so dishonest as to record under his name, experiments lacking in this elementary precaution. However, since the question has been raised by Bernthal (17, p. 172) this word of reassurance seems indicated.

animals but this does not appear to be true of normal man (161, 167, 168). Under abnormal conditions, particularly anesthesia by different drugs, the sensitivity of the center to its chemical stimulus (carbon dioxide) may be lowered more than the reactivity of the chemoreceptors to theirs, and when that happens a characteristic change in the pattern of respiratory control occurs leading to marked depression of breathing on inhalation of oxygen (161, 163 167, 168). The reflexes probably do not play an important part in respiratory control under conditions of quiet breathing at sea level but they become much more important under abnormal or emergency conditions in which the blood pO_2 or pH falls or the blood pCO_2 rises sufficiently to affect these relatively insensitive but remarkably rugged structures (161, 164, 165, 167).

This résumé of previously recorded viewpoints is given here because Bernthal (17), in his review of the subject in the preceding volume of this series, has expressed opinions which appear to this reviewer to be essentially identical with these, although they are expressly stated to be fundamentally different. Much of Bernthal's discussion involves an interpretation of our use of the term "emergency" which is quite different from that intended by us or implied in the contexts quoted by him. It is not the present reviewer's intention to devote space to an attempt to refute his criticisms because, if there is substantial agreement on the essential points involved, the subject no longer has much importance to the general reader even though one more name is added to the list (162, 164) of those who entered this field with the intention of disproving that which they eventually confirmed. Two points, however, require some comment because they have a certain amount of general importance.

The threshold of the chemoreceptors to anoxemia.—The variability in the respiratory response to anoxemia, long known and frequently commented upon (193, 206), has been noted again and again in the course of current studies related to aviation, and the reviewer can assure the reader that all variations between no hyperpnea whatever and a fairly vigorous one may be encountered in different individuals subjected to moderate diminutions in arterial oxygen saturation (down to 80 per cent). All who have had experience with work of this type emphasize the importance of psychic factors in the hyperpnea as well as in other effects (193). Therefore much greater importance should be attached to a series

of observations on carefully studied subjects whose responses are fairly well known than to single observations on otherwise unknown individuals. It happens that two pertinent studies have recently been published. In one (12) observations were made at ground level and at a simulated altitude of 15,000 feet, at which the average arterial oxygen saturation was 79.3 per cent in subjects who retained good functional activity, 77.8 per cent in those who were confused and inefficient. The corresponding values for arterial pO_2 were 42 and 40 mm. Hg. The average pulmonary ventilation in the good (unimpaired) group had increased from 9.7 to 10.98 liters per minute, while that in the poor group had risen from 8.09 to 9.36—increases amounting to about 13 and 16 per cent of the control value, a fact indicating that the hyperpneic response was certainly not marked. In the other (30), observations were made at an altitude (37,000 feet) at which some anoxemia will be present in spite of the inhalation of oxygen. Although control data were not completed at ground level, those collected at 10,000 feet on subjects breathing oxygen should suffice because the alveolar pO_2 values there were far above the normal level and the respiratory stimulant effects of subsequent diminution should therefore be more evident than usual. One subject at rest at 10,000 feet breathing oxygen had a pulmonary ventilation (calculated back to body temperature, saturation with water, and ambient pressure in each case) of 7.4 l. per min., alveolar pCO_2 of 36 mm. Hg, and alveolar pO_2 of 432 mm. Hg; at 37,000 feet the corresponding figures were 7.7, 36.8, and 76. For another there are sea-level observations while breathing oxygen, viz. ventilation 7.2 l. per min., alveolar pCO_2 35, and pO_2 653; at 37,000 feet the corresponding values were 7.4, 36.5, and 78.5. A third also breathing oxygen at rest at sea level had a ventilation of 7.8 l. per min. and his alveolar tensions were 36.0 and 668 mm. Hg; at 37,000 feet the corresponding figures were 8.5, 32.5, and 80.

Data such as these indicate that, in stable, normal subjects, the hyperpnea of anoxemia does not begin at altitudes as low as 5,000 feet and is not at all marked even at 15,000 feet under resting conditions. At higher altitudes the hyperpnea rapidly becomes more intense. The similarity of these phenomena to the contours of the dissociation curve of oxyhemoglobin, alluded to in an earlier publication (167), has been borne out by subsequent experience. The reviewer knows of no valid evidence to support Bernthal's

opinion (17) that chemoreceptor activity increases gradually and progressively from ground level upward. The recent demonstration (41, 57, 157) that the arterial blood of man at sea level is more than 98 per cent saturated with oxygen and has a pO_2 higher than 95 mm. Hg also modifies this argument.

Direct stimulation of the respiratory center by anoxia.—Here, as in the case of "emergency conditions," a difference of opinion may be synthesized from a matter of semantics when there is no actual disagreement over the fundamental facts involved. Watt *et al.* (196) found that unanesthetized dogs with denervated chemoreceptors showed in response to mild or moderate anoxemia a delayed increase in pulmonary ventilation due entirely to an increase in respiratory rate. Davenport *et al.* (50) corroborated and extended these observations and Moyer & Beecher (136) obtained similar results in dogs lightly anesthetized with pentothal. There is no doubt as to the main facts, i.e., an increase in pulmonary ventilation due mainly to an increase in rate, usually with a decrease in depth, occurring in animals in which the carotid and aortic chemoreceptors were completely denervated, and coming on after a latent period of several minutes during which breathing was depressed compared with that seen in the control period. The questions are, first, whether to call this respiratory stimulation or not, and second, what the real significance of the response may be. The answer to the first depends on the criterion adopted—whether it be a considerable increase in depth of breathing, an increase in the amount of air moved in and out of the lungs, or greater adequacy of the pulmonary gas exchange.[2] As for the second, the differences between this effect and the normal chemoreceptor response deserve emphasis. The latter comes on without appreciable latency (as seen particularly on intracarotid injections of cyanide, lobeline, acetylcholine, or other drugs that stimulate the chemoreceptors), and involves the depth of breathing more than the rate (though both are affected if the stimulus is strong enough). This other type of stimulant response involves the rate of breathing more than the depth (the depth is typically decreased), and comes on only after a latent period of at least four minutes; after the anoxemia is

[2] According to an abstract that has just become available, Margaria (125) has confirmed the accepted opinion [see Krogh, A.: *Comparative Physiology of Respiratory Mechanisms*, University of Pennsylvania Press, p. 66 (1941)] that increase in respiratory rate *per se* does not necessarily change the alveolar pCO_2.

terminated, respiratory stimulation is characteristically both marked and prolonged (50).

These findings have been interpreted (50) as meaning that anoxia, in its direct effects on the respiratory center, is both stimulant and depressant, the implication being that the stimulation is slower in onset and reversal than is the depression. This simple interpretation is complicated by experimental data of a totally different character. Chiodi *et al.* found that in the severe anoxia produced in dogs or men (35) by the inhalation of carbon monoxide the respiration was not stimulated though the circulation was, and Clark *et al.* (38) have made entirely analogous observations on dogs in which marked methemoglobinemia was produced by injections of aniline. The conclusion—that the respiratory response to anoxia depends on reflexes aroused by diminution in arterial pO_2 while in the circulatory response other agencies are concerned—is borne out by the results of artificial elevation of cerebrospinal pressure to a level higher than the arterial. As is well known (108, 166), this causes prompt failure of breathing (usually without any initial increase in depth though there may be a brief period of accelerated rate) but the blood pressure then rises toward or to the level of intracranial pressure; the result is not essentially modified by artificial respiration or by carotid and aortic denervation, though the former will prolong the period of hypertension (by preventing cardiac failure through asphyxia) and the latter will remove reflex bradycardia. But Rossen *et al.* (155), in a recent report on the effects of acute cerebral anemia produced in patients with mental disease by occlusion of the carotid and vertebral arteries, state that respiration was increased in rate and amplitude and continued to be such throughout the period of occlusion (as long as one hundred seconds) while circulation showed a notable slowing of the pulse (usually removed by atropine) without significant alteration in the blood pressure at the time of measurement (just before and just after the period of anemia); convulsions also were commonly encountered, though in briefer occlusions in normal subjects these usually came on only after the cerebral circulation was restored. These findings, in the reviewer's opinion, indicate first, that the cerebral anemia, while marked, was not total (probably because of a contribution by the spinal arteries to the basilar system inside the vertebral canal), and second, that the method employed for the occlusion (inflation of a cervical cuff with a pressure of 600

mm. Hg) elicits effects other than cerebral anemia, such as direct mechanical stimulation of carotid pressoreceptors and indirect stimulation of the chemoreceptors by cutting off their blood supply (73).

In view of these various items it is obvious that no categorical statements concerning the ability of anoxia directly to stimulate the medullary centers are justified at the present time. Perhaps the acceleration of breathing seen in denervated dogs subjected to prolonged anoxemia is related in origin and significance to the rapid, shallow breathing that has long been known to occur in clinical states involving severe cyanosis. Perhaps the cerebral anoxia produced by nonfatal amounts of carbon monoxide hemoglobin or methemoglobin was not sufficiently marked to elicit this type of response. Perhaps the increased breathing noted by Rossen *et al.* (155) was not entirely due to reflexes. In any event the accelerated breathing seen in severe, prolonged anoxemia in denervated dogs remains unexplained; it may be due to direct stimulation of the center by chemical substances produced there (which, in view of the known ability of the vasomotor center to be stimulated in cerebral anoxia, certainly cannot be excluded), to the onset or removal of afferent impulses from peripheral or cerebral regions still unidentified, or to indirect effects such as peripheral circulatory depression, epinephrine discharge, acidosis, or hyperthermia. The latter possibility is suggested by a recent report of high fever associated with exposure to severe anoxemia (194). It is not probable that hyperthermia sufficient to bring about such an effect would appear in the course of four minutes (the usual latent period in the denervated dogs) though it might be a factor in the subsequent progression of the hyperpnea (50). On the other hand, if this hyperpnea is due to an increase in effective concentration in the center of a chemical stimulant of the type concerned in normal respiratory control, some explanation must be found for the unquestioned fact that this form of stimulation involves the rate of breathing primarily while the usual physiological responses, with the single exception of those to hyperthermia, are primarily concerned with the depth. To the reviewer it seems altogether probable that, among the complex and incompletely understood changes than can be produced in nerve cells by anoxia, there is some combination that can bring about this particular type of response, but the same viewpoint was universally held with respect to the entire

anoxemic hyperpnea until the discovery of chemoreceptor reflexes forced its modification. The evidence now available indicates that the increase in depth of breathing which is most effective in decreasing the ΔpO_2 between the ambient and alveolar atmospheres, and thus in bringing into play the body's most important defense against subnormal pO_2, depends entirely on reflexes from the carotid and aortic bodies. The hyperpnea noted above clearly has a different pattern, cause, and significance but the latter two remain to be elucidated.

The effects of mechanical stimulation of the carotid sinus in man were studied in one hundred subjects, twenty-six of whom were sensitive and seventeen regularly showed convulsions (73). Immediate apnea (the response typical of stimulation of the carotid pressoreceptors by elevation of intracarotid pressure in laboratory animals) was never observed; reasons are given for believing that this is because the carotid body receptors were simultaneously stimulated. The existence of the "cerebral type" of reaction (i.e., syncope and convulsions without marked changes in the systemic circulation) was confirmed.

Other Reflexes

Wyss (205) continued his studies of the respiratory effects of stimulation of the vagus of the rabbit at different frequencies and presented further evidence in support of a reciprocal innervation between the inspiratory and expiratory centers, against the existence of two sets of receptors and afferent fibers to the respiratory center in this nerve.

Petitpierre (148) investigated the reflexes said (by Fleisch) to be produced from the respiratory passages by changes in pressure within them and concluded that these reflexes cannot arise from, or be transmitted through, the upper respiratory passages (larynx, pharynx, nose, and mouth). There were signs of a reflex aroused from bulging of the epiglottis and the lower part of the pharynx, but the pressures required (12 to 16 cm. water) were too great to have physiological significance. The other parts were insensitive to pressure. Continuing this investigation he (150) found that the Fleisch proprioceptive reflexes persist in cats after interruption of all afferent pathways (vagi, cervical sympathetics, third to eighth cervical dorsal roots inclusive, and transection of the cord below C8). The same denervation procedures also did not prevent the in-

crease in electrical activity, in one phrenic nerve, when the other was cut (150). The peripheral end of the superior laryngeal nerve of the rabbit was found (149) to show rhythmic activity synchronous with inspiration; this did not occur in cats, in which the extrinsic muscles of the larynx do not participate in the respiratory act, and the conclusion was reached that the impulses found in rabbits come from the laryngeal muscles, not from the mucous membrane (149).

Reid & Brace (152) also investigated reflexes from the upper respiratory passages (of the dog). The results were quite variable but the authors interpret them to mean that stretching of the muscles of the neck, tongue, mouth, pharynx, trachea, and esophagus gives rise to reflexes stimulant to heart rate and to respiration. The effects from the trachea (probably) and esophagus (certainly) are said to persist after vagotomy. In view of these and the other related observations that have recently been reported (148, 150), it would appear that the reflex machinery of the air passages is much more complicated than had been realized.

Grandjean (88), from electrical stimulation of the central end of the phrenic nerve in rabbits and cats, concluded that the responses thus elicited probably are not specific but are simply due to involvement of pain fibers.

Martin *et al.* (127) stimulated the celiac ganglion in six patients in the course of operations for sympathectomy. Systolic blood pressure rose by 18 to 46 mm. Hg and breathing first ceased (usually in the inspiratory position), then began again, as a rule at a more rapid rate. Stimulation of the central end of the splanchnic elicited the same type of response but a more marked one. These effects, essentially sympathomimetic, are entirely unlike the depressor reactions to traction on the viscera (127).

The Respiratory Center

Opposing views as to the interpretation of the evidence available on the location and functional integration of this structure will be found in the three preceding volumes of this series (17, 76, 168). As far as the reviewer knows, no cogent evidence bearing on these points has been submitted during the past year. Meier & Bucher (131) found evidence of the existence in the pons (of the rabbit and cat) of mechanisms capable of inhibiting the influence of afferent vagal influences on respiration; the effect showed species variations, being exerted mainly on the inspiratory vagus effect in the

cat, the expiratory in the rabbit. The relation of this to the so-called pneumotaxic center is not clear to the reviewer. The authors include a theoretical electrical schema said to be capable of explaining all spontaneously occurring or artificially induced changes in the rhythm and type of breathing. Lewis *et al.* (117) report findings which suggest that a sustained inspiratory effort can involve the cardioinhibitory center.

Two excellent studies on the innervation of the respiratory muscles were reported. One (78) demonstrates a striking parallelism between the respiratory rates of different species (horse, dog, rabbit, rat, and mouse) and the frequency of the electrical activity in the diaphragm at inspiration; the underlying mechanisms of reinforcement and recruitment are discussed from the teleological point of view. The other (151) deals with an attempt at elucidating the phenomena associated with the integration of these processes in the central nervous system; evidence is presented to indicate that the activity of the respiratory center is associated with a refractory phase proportional in degree and duration to the strength of the activity, and that the rhythm of the center will depend on the balance between the excitation and the excitability existing at the moment.

Periodic respiration was taken up from the theoretical viewpoint by Bethe (18), who points out the frequency with which this type of activity is encountered in living systems. He presents an electrical schema by which these phenomena can be duplicated more or less faithfully. Christie & Hayward (36) report findings (in cats) that support the belief that periodic breathing in cardiac disease may depend in part on rhythmic changes in pulmonary vascular tone.

Drug Actions

The effects of various drugs on the tolerance to anoxia have already been considered (p. 252), as have recent studies bearing on the cholinergic conception (p. 241).

Henderson & Yi (97) studied the effects of depressant and stimulant drugs on the respiration of the rabbit and concluded that nikethamide, metrazole, strychnine, caffeine, and picrotoxin act mainly if not exclusively on the respiratory center, not on the chemoreceptors. Abreau & Woodbury (1) found that the circulatory effects of strychnine convulsions in dogs are variable and

that respiratory failure is due more to asphyxia than to direct or reflex effects by the drug. Bucher (27) investigated the actions of morphine in rabbits, as did Henderson & Yi (97), and concluded, from the effects of transections of the neuraxis at different levels, that the main effect of the drug on respiration is to release the expiratory vagal mechanisms at the caudal end of the pons, either by blocking inhibitory influences previously exerted upon them or by actually stimulating them. Bulbring & Whitteridge (28) found (in spinal cats) that volatile anesthetics caused first an increase, then a decrease in the electrical activity of single fiber vagus preparations during constant artificial respiration; anesthetic gases (nitrous oxide, propylene) only increased the activity and barbiturates only decreased it while nitrogen did not affect it at all. Picrotoxin was found (197) able to increase the excitability of the cat's respiratory center (judged by its response to direct electrical stimulation) for long periods of time (average seven and one-half hours) after a single dose of 0.25 mg. per kilogram, but picrotoxin had only a depressant action on the uptake of oxygen by brain homogenate *in vitro* (113). Schmidt *et al.* (170) found in monkeys that cerebral oxygen uptake and blood flow both increased during convulsions (produced by metrazole or picrotoxin) and decreased under the influence of a depressant (pentothal); the decrease associated with temporary abolition of reflex activity and depression but not complete paralysis of respiration was of about the same order as that seen in the depressed phase after convulsions. Figures for arterial oxygen saturation and tension in human subjects under nitrous oxide anesthesia are given by McQuiston *et al.* (130). With the oxygen content of the inspired air between 31.3 and 21.8 per cent the saturations ranged from 97.5 to 89.0 per cent, the tensions from 90 to 56 mm. Hg. An added pressure of 10 to 15 mm. Hg produced no significant increase in the oxygen or nitrous oxide content of the blood. It was concluded that no serious anoxemia is likely to be encountered if the inspired air contains 20 per cent or more of oxygen, but that at 12 to 15 per cent oxygen dangerous asphyxia is likely to occur. These findings include more or less heavy preoperative sedation, which would doubtless have depressed the respiratory center.

The effect of single large (0.1 gm. per kg.) doses of various sulfonamides on the respiratory functions of the blood was studied in dogs by Hall (92). All of the drugs used lowered the oxygen

capacity somewhat but the effects on carbon dioxide capacity were neither consistent nor marked. No significant amounts of abnormal pigments were seen with any of them and there were no marked changes in the acid-base balance.

The effects of various drugs on the circulation in the upper respiratory passages was studied by Jackson (107).

STUDIES ON THE BLOOD

Recent developments bearing on the normal oxygen saturation and tension of arterial blood have been described above (p. 231)

Fetal blood has been investigated by several groups who have concluded that the adult and fetal forms of carbonylhemoglobin consist of at least two molecular species the relative proportions of which differ markedly in the two states (4); that the carbonic anhydrase content of fetal blood is much lower than that of the adult and rises rapidly after birth (182); that the oxygen saturation of fetal blood decreases rapidly at the end of the period of gestation (13); that in man, unlike other species, fetal blood has a lower affinity for oxygen than maternal blood because of some still unknown property of the maternal erythrocyte (128). Studies of blood drawn from the umbilical cord during Caesarean sections are reported by Dieckmann *et al.* (55).

Methemoglobin formation has been studied by aniline (38), nitrate (89), and ferricyanide (84). Ascorbic acid reduces methemoglobin formed either by nitrate or ferricyanide, the former more slowly than the latter, because of a catalytic effect by ferrocyanide on the reduction of ferric ions (84). The question of the occurrence of significant amounts of methemoglobin in the arterial blood of normal man has been considered above (p. 232).

A method for calculation of the oxygen dissociation curve in the presence of carbon monoxide hemoglobin has been presented (156).

CLINICAL STUDIES

Only those having importance to fundamental respiratory physiology are considered here.

The functions of the normal and abnormal lung.—Hall & Wilson (93) found that at least half of the tidal volume is inspired at rates of 80 per cent of the peak velocity or higher, at rest and during work.

The basal metabolic rate records of five hundred female and two hundred male subjects were analyzed by Caughey (32), who derives from them a set of constants for the average rate, depth, ventilation, pattern, and variations to be expected among a group such as this. Darling *et al.* (47) studied the mixing of gases in normal and emphysematous lungs by means of estimating the rate of removal of nitrogen during oxygen inhalation; they concluded that while some normal lungs display nearly perfect mixing, others do not; emphysematous lungs showed striking unevenness of mixing. Determination of the components of the air in the lungs at rest and during moderate exercise was found by Hannon (95) to be the most accurate means of determining the degree of disability associated with pulmonary fibrosis; the most striking difference between the normal and the silicotic lung is that with the latter the demand for increased pulmonary ventilation must be met by increasing the rate since the capacity for increasing the depth is greatly restricted. The influence of posture on the partition of air in the lungs was studied by Altschule and his collaborators (3) in patients with congestive heart failure, with the surprising result that the changes seen were less rather than greater than those seen in normal subjects; the orthopnea of heart disease therefore must depend on a summation of many influences, some of which are cited. They (2) also investigated the effect of removal of fluid from the pleural cavity and found that complete re-expansion of the lung did not occur for three to four weeks; the immediate relief of dyspnea that was seen in all cases therefore was not due solely to overcoming atelectasis; the fluid apparently displaced mainly the complemental air and therefore interfered with increase in respiratory depth on exercise. Hofbauer (102) found that after the immediate relief associated with removal of purulent fluid from the chest, dyspnea is likely to ensue; it is markedly worse in the recumbent position and is probably due to atelectasis and emphysema. Banyai & Jurgens (10) report favorable results from the use of carbon dioxide inhalations in the treatment of pulmonary tuberculosis.

Relations of respiration and circulation.—Mackay (122) studied the influence of posture on alveolar ventilation in normal subjects and found that alveolar pCO_2 fell on the change from recumbent to erect, rose on the reverse change; the change could not be accounted for entirely by alterations in pulmonary ventilation and,

from experiments involving inflatable cuffs and bandages, it was attributed mainly to changes in the effective volume of blood to which the gases are exposed in the lungs. Perera & Berliner (146) concluded that one of the reasons for the onset of attacks of paroxysmal dyspnea at night is the return to the blood stream of fluid lost from it during the course of the day's activities. The studies by Galdston *et al.* (73) on carotid sinus reflexes in man have already been noted (p. 261). Battro *et al.* (14) investigated the changes in blood pressure associated with the respiratory cycle and found them inconstant in both direction and extent unless the breath is held; in the Valsalva maneuver the events were found to occur in three stages, viz., an initial fall in systolic and rise in diastolic pressure with slight increase in pulse rate, then a fall in both systolic and diastolic pressures, and (after release of the strain) a rise in both pressures above normal with bradycardia.

The hyperpnea of muscular exercise has been the subject of a recent review by Comroe (40) and the reviewer has nothing to add to the discussion there presented except to note the recent report by Delucci (54), who found that a partial obstruction to the circulation in the lower legs that would cause only an insignificant increase in pulmonary ventilation at rest, led to a distinct increase when superimposed on pressure by the feet against a continuous load of twenty pounds. The results have practical bearing on the influence of tight boots on oxygen economy in airplane pilots; they also add to the reasons for suspecting that peripheral chemoreflexes may be involved in the hyperpnea of exercise in spite of the past lack of success in demonstrating such a relationship (40).

Ciliary activity.—According to Hilding (99) the ciliated epithelium becomes replaced with mucus-producing cells in severe asthma and bronchopneumonia and this viscid secretion plays a part in a fatal outcome. Boyd *et al.* (25) in a study in animals found that in the absence of ciliary activity the normal respiratory passages could absorb large amounts (2 cc. per Kg. per 24 hr.) of fluid but that this capacity was greatly lessened by pulmonary disease.

The breath-holding syndrome in infants is discussed by Bridge *et al.* (26). Hamilton & Mayo (94), from studies of the effects of immersion in water and of cutting off the limb circulation by inflatable cuffs, confirmed the current belief that the vital capacity is subject to modification by displacement of blood from the systemic into the pulmonary circulation; an interesting finding was

that a man may be unable to inhale after exhalation under water presumably because of a reflex similar to that seen in diving animals.

METHODS

Scholander and his collaborators have developed a modified tuberculin syringe for the analysis of oxygen (158), carbon monoxide (174), nitrogen (59), and carbon dioxide (175) in volumes of blood of the order of 0.4 cc., as well as a more flexible micrometer burette (173). The reason for the low figure for blood oxygen yielded by nonvacuum devices such as the Barcroft differential manometer, according to Gibson (85), is an uptake of oxygen by the plasma when it is alkalinized with ammonia; if ferricyanide is used in neutral solution the results agree fairly well with those obtained by the Van Slyke method. Horecker & Brackett (104) report a rapid spectrophotometric method for determining methemoglobin and carbon monoxide hemoglobin in blood; the accuracy claimed is within about 1 per cent of the Van Slyke procedures. Chase *et al.* (33) describe a method for determining methemoglobin, oxyhemoglobin, and hemolysis in about 0.7 cc. of blood. Iliff *et al.* (105) present a simple method for the approximate analysis of carbon dioxide and oxygen in gaseous form. Stadie & Riggs describe methods for studying the gaseous metabolism of tissues under high pressures of oxygen (179) and for the convenient and accurate preparation of tissue slices for such studies (180). A glass electrode suitable for use with amounts of fluid as small as 0.005 cc. is described by Claff & Swenson (37). Cohn (39) reports a method for the determination of hemoglobin in tissue extracts and other turbid solutions with a sensitivity corresponding with about 1 mg. of hemoglobin. Finesinger (68) describes a procedure for making and scoring spirograms in psychiatric patients and Margolin & Kubie (126) describe an acoustic respirograph. Methods of artificial respiration are discussed by Cordier (43) and by Waters (195). Kreiselman (114) presents a simple apparatus for resuscitation and Maloney (123) gives a report (obviously preliminary) of experiments with a mechanical device (the Revair Aerophore). Steinberg & Dietz (181) compared mechanical and manual resuscitation procedures in dogs and found the former more successful. Thompson & Birnbaum (185) report on resuscitation by rhythmic inflation of the lungs with nitrogen; they believe the favorable results to be due to reflexes, mainly from deflation of the lungs.

Barach *et al.* (12) describe their technic for measuring altitude tolerance and conclude that general impressions by trained observers of the behavior of the subjects is the best all-around criterion. Von Tavel (193) outlines his corresponding procedures and comes to quite different conclusions. Such differences of opinion are typical of the present status of this subject.

Notable books include a translation of Paul Bert's *Pression Barometrique* by the Hitchcocks (101) and Barach's (11) description of inhalation therapy. These as well as von Tavel's review (193) contain good historical summaries of the development of aviation physiology.

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MUSCLE

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Introduction

During the past two years investigation in the field of muscle physiology has been very largely limited to those aspects of the subject which have obvious practical applications. The efforts of physiologists studying muscle have thus been directed along several well-defined lines. This imposes a limitation of subject matter on a review already geographically circumscribed by the fact that many important European scientific publications are either nonexistent or are not available in North America.

Histologically and functionally all contractile tissue falls into three classes, smooth (sometimes called nonstriated or involuntary), striated (sometimes called striped, skeletal, or voluntary) and cardiac muscle. As the physiology of smooth muscle has been reviewed recently by Fischer striated or skeletal muscle will be taken as the chief subject of the present review. Little work has been done recently on cardiac muscle so it will not be considered separately but will be compared with skeletal muscle where new information is available. An attempt has been made to cover investigative work reported between August, 1942, and September, 1944, and earlier work is mentioned only when it was not available to the previous reviewer or is essential to a logical treatment of later work.

Unfortunately, knowledge in the field of muscle biophysics is not as yet sufficiently far advanced to permit the reviewer to follow any functionally reasonable plan in the presentation of the new findings. Investigative work dealing with the physiological properties of normal innervated mammalian skeletal muscle will receive first attention under a number of arbitrary headings. Following this the myoneural junction will be treated and in this section will be found all work dealing with the relation of the neurohumors and neurohumoral mechanisms to skeletal muscle functions. The consideration of the clinical applications of our knowledge of muscle biophysics, which has received much attention

lately especially as it relates to denervated skeletal muscle, will be left to the end.

The Physiology of Innervated Skeletal Muscle

A complete study of the physiology of a tissue must include a consideration of both the chemical and physical properties exhibited by that tissue, indeed must embrace the fields of biochemistry and biophysics. However, as has been the custom in these reviews in the past, the chemical properties of muscle will not be considered except insofar as they are directly related to its physical properties.

Structural properties.—The mechanical aspects of muscular activity interested the ancients. Galvani performed biophysical experiments on skeletal muscle tissue which are familiar to all physiologists. In spite of this early start at the investigation of the physical properties of muscle it was not until the fundamental work of Astbury (1), recently reviewed and extended by Verzár (2), that physiologists could give any explanation for the fact that the muscle fibres shorten when suitably stimulated. Astbury first postulated and later demonstrated the fundamental physical changes in the myosin molecule which are responsible for this shortening. His work explained the mechanism of the shortening but threw no light on the nature of the excitatory process by which the physical changes in the myosin molecule are initiated. Singh (3) has carried forward a comparison of the behavior of the myosin molecule *in vitro* and as a functional part of the intact muscle cell. Although unstriated muscle was used in most of his work a reasonable and useful comparison between the function of myosin in this tissue and in striated muscle was made. The contraction of myosin in muscle induced under similar conditions suggests the possibility that muscle can contract without consuming oxygen. Singh has also pointed out that if the normal contraction of muscle be due to the physical change of myosin molecules within that muscle then the internal friction between the molecules would increase when the muscle contracts and the viscosity of the muscle would be raised thereby. Such an increase in viscosity should be abolished by stretching the muscle as this would reverse the intramolecular "bunching" induced by the contraction. He has shown that these phenomena occur as predicted. Roentgen-ray diffraction studies of the parallel fibres of sartorius muscles of *Rana pipiens* have been

reported by Spiegel-Adolf and co-workers (4). The findings of Astbury and other earlier workers were verified and much new information obtained on changes accompanying mechanical and electrical stimulation and the application of rigour-producing procedures.

The phenomenon of birefringence is exhibited by muscle tissue to a degree not seen in other body tissues and may be shown to be related to the microscopic and submicroscopic structure of the contractile mechanism as was pointed out by Fischer (5) in the preceding review on this subject. The total birefringence of muscle may be divided into two parts, "form" birefringence being due to the parallel arrangement of the micellae and accounting for about 65 per cent of the observed effect and "crystalline" birefringence being due to the myosin molecules in the micellae and accounting for the remaining 35 per cent of the birefringence. Fischer (6) cites these figures as averages obtained from a variety of striated and smooth mammalian muscle fibres. He has shown that stretching the resting striated muscle fibre increases its birefringence by about 4 per cent for 25 per cent elongation. The birefringence was found to diminish during a tetanic contraction and was little changed by an isometric twitch. Prediction would be that "form" birefringence remains unchanged when the dimensions of the muscle fibre are not permitted to alter during activity as in the case of isometric contraction. It is a point of considerable interest, however, that the molecular structure of the myofibrils also apparently remains unchanged during the isometric type of contraction. Tension produced apparently results from attraction between side chains of the myosin molecule with no spatial alteration in the configuration of that molecule. The so-called isometric contraction is thus apparently truly isometric in that it involves no movement of the components of the myosin molecule.

Fischer (6) has further shown that stretching striated muscle increases the "crystalline" birefringence more than the "form" birefringence while in smooth muscle the "form" birefringence is affected more than is the "crystalline" birefringence. Due probably to the greater extensibility of smooth muscle the changes observed on stretching are greater in smooth than in striated muscle. Indeed, for lengths which are still physiological, more marked birefringence has been observed in stretched smooth muscle than has ever been found in striated muscle under any conditions.

X-ray diffraction and visible light refraction studies have thus yielded certain indirect information concerning the physical structure of striated muscle. Various attempts have been made to get direct evidence as to the nature of the "fine" or so-called submicroscopic structure of muscle tissue. Notable among these is the work of Lavin & Hoagland (7), in which an improved technique of ultraviolet light microscopy has yielded photomicrographs showing a greater detail of the myofibrillar structure than any direct pictures obtained heretofore. Direct evidence as to the nature of the myofibrillar or micellar structure of striated muscle awaits the employment of techniques not yet perfected. Examination of single muscle fibres under the electron microscope should yield valuable information especially if steps could be taken to flatten the muscle fibre so that a single layer of myofibrils would lie in the plane parallel to the electron beam. It is surprising that the past two years have yielded no report on work of this nature.

Mechanical properties.—Muscle tissue is unique among the tissues of the body by virtue of its ability to shorten and thereby to do mechanical work. Much of the investigation considered under the head of "structural properties" might logically be considered with the "mechanical properties." Under this head we will include the various manifestations of the contraction process.

Elftman (8) has achieved a short but remarkably complete review covering the mechanical properties of skeletal muscle and the bony skeleton in man and the manner in which these are interrelated for the purpose of utilizing the contractile properties of muscle tissue for the purpose of producing bodily movement. Our knowledge of even the elementary facts of muscle mechanics is far from complete and the investigative work reported during the past two years has done little to improve this situation. It is unfortunate that this branch of biophysics has been neglected by research workers. The orthopedic surgeon faced with the problem of repairing battle-damaged skeletal and muscular systems could make effective use of a much more complete knowledge of muscle mechanics than is at present available.

Wills (9) has investigated the speed of responses of various muscles in cats but the number of peaks of negativity found in a record of the action potentials of any one muscle showed no definite relation to the number of peaks of tension appearing in the myogram. There was a general parallelism between the speed of con-

traction of a muscle and the frequency of motor nerve stimulation needed for effective activation of the neuromuscular system. This type of investigation can be carried out with ease on experimental animals but offers the greatest difficulty when man is taken as the subject. In the human subject we can only measure the physical results of the activity of groups of muscles. Heretofore even these gross examinations have been possible only on the extremities. Mayer & Greenberg (10) have described methods for the measurement of the strength of trunk muscles. Such methods, coupled with the adequate use of electromyographic techniques designed to indicate the muscles involved in the movement under study, may yet lead to a sound knowledge of the manner in which skeletal muscles bring about skeletal movements in the intact human animal.

Tone is one of the important mechanical properties of skeletal muscle. Jacobson (11) has reviewed his study of tonus covering a period of fifteen years. Most of the investigation has been done on man although some observations have been conducted on dogs, frogs, and rabbits. He points out that the electrical concomitant of contraction or tonic activity will be missed unless amplifiers designed for adequately low frequency and low voltage measurement are employed. His findings show that in more than three hundred instances in man and in many experiments on the frog and dog, muscles are often so relaxed that they reveal no action potentials. This finding lends no support to the view, held by many, that during health striated muscles in mammals are always in a state of tonus or partial contraction which may be slight but is sufficient to promote the return of venous blood to the heart. Jacobson's work, however, confirms the traditional view that healthy muscle usually shows a state of slight contraction and that even during ordinary states of rest, including sleep, action potentials frequently can be detected with instruments of sufficient sensitivity.

Before full agreement with Jacobson's thesis could be admitted evidence would have to be provided that the sensitivity and frequency response characteristics of the electrical recording system used were adequate to ensure detection of the activity of a single motor unit whose muscle fibre components lay at some distance from the electrodes used. This question of the adequacy of the recording system has always arisen in connection with electromyo-

graphic studies of muscle tone. Indeed, Jacobson (12) questions part of the work of Hoefer (13) on just these grounds although, in the main, the findings of these two investigators agree. It would be interesting to test the recording system used in work of this nature by making observations on experimental animals using a single motor unit excitation obtained by cutting down the motor nerve to a single fibre in the manner described by Adrian & Bronk many years ago. Many such preparations would have to be made and the equipment tested for its ability to give a record of the activity resulting from a single impulse in a single motor nerve fibre.

Henderson (14) has reviewed the literature covering the relation of muscle tone to the venopressor mechanism. Much of this review is devoted to matters needing further elucidation. Considerable evidence is presented in support of the author's thesis that the tone of skeletal muscle is an essential fact in the maintenance of the circulation. He believes that skeletal muscle tone and its variations transmitted as intramuscular or tissue pressures furnish the basis of a venopressor mechanism which may be as important to the circulation as is the heart itself. It is claimed that a large percentage of all deaths are due to a failure of skeletal muscle tone which, by permitting stagnation of the blood in the venous system, brings the circulation to its final and fatal standstill. Obviously there is serious need for further experimental work to determine the relation of skeletal muscle tone to intramuscular or tissue pressure and the relation of both these factors to venous pressure.

Gunther and co-workers (15 to 21) have described a method for the simultaneous measurement of intramuscular and venous pressures. They have measured these pressures in man under a wide variety of conditions. They conclude that venous pressure is not a determinant of intramuscular pressure but that the maintenance of intramuscular pressure is necessary to normal peripheral circulation. A fall in intramuscular pressure has been observed to precede the onset of surgical shock. Hathaway & Moore (22) deny that intramuscular pressure gives any useful indication of the onset of shock in men or dogs.

A variety of problems related to muscle tone have received recent attention from investigators. Singh (23) has investigated the viscoelastic constants of unstriated muscle and compared them with the same properties in striated muscle. These properties have

an obvious relation to muscle tone. It can be shown that the limb muscles of man exhibit hypertonus following a contraction and Wells (24) claims that acoustic stimuli modify this hypertonus in a bizarre manner. Wenger (25) has outlined an attempt to appraise individual differences in the level of muscle tone using a simple method of factorial estimation which he concludes affords the most adequate technique for the measurement of general muscle tension yet devised. Kiely, Hamilton & Gellhorn (26) have shown that hemorrhage, in unanesthetized decerebrate dogs, gives rise to an increase in muscle tone which is reversed on the reinfusion of the blood lost. This rise in muscle tone is seen even when the fall in blood pressure is prevented by the simultaneous injection of ephedrine. Bozler (27) has been able to demonstrate tonic contraction in resting cardiac muscle and has found that a rise in tone is accompanied by an increase in metabolism and a decrease in surface polarization. These changes occur as part of the process leading up to a contraction. They are linked with the properties of automaticity and rhythmicity of contraction which are a feature of this tissue.

Psychologists have made efforts from time to time to study the relation between muscle tone and psychic tension. Again the difficulty of making muscle tone measurements in man has seriously interfered with experimental work. Arnold (28) has attempted to correlate muscle tone with the breakdown speed of manual tapping and of writing shorthand from dictation. The breakdown speed was highest in subjects showing a high muscle tone. Kretschmer (29) has discussed muscle tone and its relation to a wide variety of bodily functions. Although a great many of his hypotheses are farfetched and the great body of his statements are unsupported by any experimental evidence his ideas are interesting and provocative. It might be argued that this aspect of muscle tone, namely its relation to the function of other parts of the body such as the endocrine glands and the various parts of the central and autonomic nervous systems, is not the proper concern of the physiologist. This is almost certainly a mistaken attitude and it is probably this attitude which has resulted in our lack of precise knowledge concerning the role played by skeletal muscle tone in the intact human organism.

Chemical properties.—The chemical aspects of muscle physiology will be considered insofar as they affect excitability and the

other biophysical aspects of the contractile process. The complex cycle of chemical reactions involved in the release of energy in the contractile process will not be considered. In short, we will be concerned with the inorganic and not with the organic chemistry of the muscular contraction.

Miller (30) has shown that potassium, phosphorus, and sometimes nitrogen exhibited a relative increase within the muscle cell following the partial depletion of extracellular electrolytes. Alterations in muscle electrolytes were accompanied by an increase in the concentration of potassium in the serum. The changes were independent of any kidney activity and Miller suggests that they were due to some unidentified substance released from muscle. Although all the experimental work was done on rats this study indicates that the rise in serum potassium observed clinically in burns and other shock-producing injuries may be related to the loss of organic substance from the muscle cell which accompanies depletion or immobilization of extracellular fluid.

Crismon and co-workers (31) have studied electrolyte redistribution in cardiac and skeletal muscle in potassium poisoning in the cat. Potassium was administered until potassium poisoning could be diagnosed on the basis of disappearance of the P wave from the electrocardiogram. Both cardiac and skeletal muscle were found to take up potassium readily when the potassium content of the environmental body fluids was raised. This occurred even when the potassium concentration in the body fluids was at a level considerably below that found within the muscle fibres. Uptake of potassium by the heart was associated with a loss of sodium and the appearance of considerable quantities of chloride in the intracellular fluid. The change in the electrocardiogram represented an alteration in the function of cardiac muscle although no change in the functional characteristics of skeletal muscle was reported. Thus in potassium poisoning we see a migration of potassium into the muscle fibre and under other conditions, notably those resulting in damage to the muscle fibre membrane, migration of potassium from the fibre can be detected.

Rewell (32) has shown that a rise in potassium concentration in the blood stream follows ischemia of skeletal muscle. It is probable that this potassium has come from muscle cells in the ischemic area although it might have been released from the liver by the action of some hypothetical substance arising in the damaged limb tissue

(33). The work of Pen and co-workers (34) would indicate that traumatized muscle releases potassium. It is probable that this occurs whether the damage to the muscle membrane is produced by anoxia or by physical forces. These workers have made a variety of different types of muscle extracts and found no substance other than potassium which could be considered toxic in nature. It is well known that a high concentration of potassium within the muscle cell is necessary for the normal functioning of that cell but it now becomes apparent that this reservoir of potassium constitutes a potential hazard to the rest of the body which is protected from this toxic material by the normal intact muscle cell membrane.

Greville & Lehmann (35) have demonstrated a magnesium-calcium antagonism in muscle. Magnesium narcosis is well known and the administration of magnesium sulphate is used clinically to produce mild degrees of narcosis or anesthesia. Accompanying this anesthesia is a muscle paralysis which apparently appears due to the direct effect of magnesium on the muscle cell. This paralysis, like all magnesium effects, is antagonized by calcium. It is well known that potassium leaking from a muscle cell into the intracellular fluid will produce inexcitability of the cell unless provision is made for removing the excess potassium from the environmental fluid and it has been shown that calcium, to some extent, antagonizes this process. The effect of magnesium on muscle cell potassium and on the migration of potassium through the muscle cell membrane is not known.

In spite of the difficulties in potassium estimation Wilde (36) has been able to show that potassium entering the skeletal muscle of albino rats is accompanied by chloride. This is important because the entrance into the fibres of potassium as potassium chloride from intracellular fluids high in potassium and low in sodium entails the entrance of water into the muscle cell for the maintenance of osmotic equilibrium. Entrance of potassium alone in exchange for sodium would involve no water shift. Heilbrunn & Hamilton (37) have indicated the pitfalls attendant on employing the ordinary methods for the estimation of chloride to the analysis of muscle tissue.

Conway & Fearon (38) have studied the acid-labile carbon dioxide in mammalian skeletal muscle and estimations made on the basis of these determinations indicate that the hydrogen-ion concentration within the resting muscle fibre is around pH 6.0. The

hydrogen-ion concentration within the muscle cell depends, to an extent related to the buffering power of the muscle protoplasm, on the intracellular fluid, the composition of which in turn reflects the adequacy of the blood supply to the muscle. Grosse-Brockhoff, Rein & Schoedel (39, 40) have made a progress report on the relation between blood supply to muscle and its working capacity. It is impossible to detail the findings here but it has been shown that a definite minimal carbon dioxide tension in the blood must be maintained if the muscle is to work efficiently. Even in the presence of hyperemia with adequate oxygen saturation of the tissue fluid it has been observed that high carbon dioxide tension leads to a limitation of the efficiency of the working muscle. Wallace & Lowry (41) have also studied the role of carbon dioxide in mammalian muscle and have found muscle fibres *in vitro*, and inferentially *in vivo*, to be highly impermeable to the bicarbonate ion. Lorber & Evans (42) studying the effect of gaseous interchange on isolated mammalian cardiac muscle find that anoxia depresses isolated cardiac muscle only at oxygen tensions well below those which could be tolerated by the intact animal, or at high carbon dioxide levels. The effect of carbon dioxide on isolated cardiac muscle appears to be due chiefly if not entirely to the resulting change in hydrogen-ion concentration.

Fatigue is an important property of muscle tissue and is certainly chemical in nature. Fatigue as seen in the intact animal body is a complex phenomenon involving the central and autonomic nervous systems as well as muscle tissue. Our only concern here is with true muscular fatigue. Scheinfinkel (43) has shown that even muscle exhibiting a high grade of fatigue as the result of direct stimulation shows no damage to its contractile apparatus and no detectable exhaustion of its store of energy-yielding chemical substances. Gerson (44) believes that fatigue is due to a change in the mineral metabolism of muscle. He states that thus there may be an actual depletion of available potassium, phosphorus, calcium, and magnesium and that these substances should be abundant in the diet to combat fatigue. The evidence offered in support of this hypothesis is not entirely satisfactory. Fatigue probably occurs as a direct result of the accumulation of metabolites (45). These appear diffusely through the muscle fibres although there is some indication that it is their presence in the vicinity of the end-plate which is chiefly responsible for the phenomenon of fatigue. Some believe that accumulated metabolites interfere with neurohumoral

mechanisms at the myoneural junction and others maintain that fatigue is the result of interference with the intermediary metabolism in the muscle fibre. Staub (46) in a review on "The Pharmacology of Fatigue" and more recently Harpuder (47) present the evidence for both views. It is quite possible that both processes occur and are jointly responsible for muscular fatigue.

Jakowlew (48) has shown that muscular fatigue in the intact animal can be carried to such a point that there is a reduction in the power of the muscle to do work which outlasts the immediate recovery from fatigue and indeed may amount to semipermanent if not permanent damage to the muscle. Simonson and co-workers (49) have shown that there is an optimum rate for muscular work. Short, moderate exercise of a muscle stimulates the further activity of that muscle whereas severe muscular exercise acts as a depressant. The authors believe that these effects are produced on the central nervous system although there may also be a direct action on the muscle itself. The phenomenon of "treppe," which is simply a demonstration of the beneficial effect of repeated muscular contractions on subsequent contraction, can be readily demonstrated in cardiac muscle and may, as these experiments indicate, also be seen in skeletal muscle.

Diet has an obvious relation to muscular fatigue in that the foodstuffs must provide the energy for muscular contraction. However, Henschel (50) claims that although special benefits from special foods have often been claimed there is little evidence that muscular activity can be influenced by the addition of any special materials to a diet which is already normal and adequate by present-day standards. The claim that the ingestion of gelatin can delay the onset of muscular fatigue has not been borne out by the work of Horvath (51). Potter (52) has studied the role of vitamins in the energy transformation in skeletal muscle and concludes that most of the B vitamins, probably as the prosthetic groups of specific enzymes, are required for this complex chemical process. Hulse and co-workers (53) have made observations on the level and function of thiamine in skeletal muscle of infants and children in subclinical vitamin deficiency and conclude that such deficiency can be detected, on occasion, by the low level of the vitamin in muscular tissue. The role of vitamin E in muscle physiology is a matter of controversy and is treated later in connection with certain clinical considerations.

When voluntary power is returning after a peripheral nerve

injury the type of fatigue seen in the recovering muscle resembles that observed in myasthenia gravis and for this reason Götze (54) has investigated the action of prostigmine in a series of twenty-two cases. In cases where the denervation was not unduly prolonged the drug prolonged the period of exercise which could be tolerated before fatigue was observed. The drug seemed most effective at the time when voluntary power was just returning and it is thought that its use at this time might shorten the period of convalescence.

Electrical properties.—This branch of muscle physiology may be divided into two parts. First, there is the study of the electrical concomitants of the muscular contraction, the so-called action potentials which accompany muscle fibre activity. The second part includes all the phenomena associated with the electrical stimulation of muscle tissue. The study of action potentials and the various manifestations attendant on the electrical excitation of muscle tissue have interested physiologists for many years. Recently, however, clinicians have become fired with the possibilities of the various electrodiagnostic procedures including studies of muscle action potentials under the name "electromyography." Electrical excitation has been used for many years for diagnostic purposes but is coming into more widespread use both for diagnostic and treatment purposes. As a result of this clinical interest and enthusiasm most of the recent research work on the electrical properties of muscle has been performed with practical application in mind. This is natural at a time when trauma to motor nerves is yielding a large body of clinical material. The various properties of denervated muscle and the electrodiagnostic and treatment methods which may be used on this tissue will be considered later in this review. The electrical properties of innervated muscle will be dealt with here.

Toman & Oster (55) have confirmed the accepted view that the simplest possible voluntary movement results from a single excitation of a single motor unit. Stronger twitches result from the synchronous or overlapping discharge of two or more units or from the serial discharge of two or more units. These conclusions have been reached by the use of the muscle action potentials as an indication of contractile activity. Gesell & Atkinson (56), investigating the contractions of the diaphragm of the mouse, rat, rabbit, dog, and horse, have demonstrated characteristic elec-

trical patterns of multifibre twitching. They have obtained evidence which indicates that the mechanism by which the gradation of contraction strength of muscle is achieved involves the recruitment of reserve muscle units rather than the variation in twitch frequency of these units. Great care has to be taken in interpreting the activity of a motor unit on the basis of action potential observation, since mono-, di-, tri-, and polyphasic action currents from single motor units have been observed by Denslow & Hassett (57). The pattern of the discharge is apparently influenced by the type and the location of the electrode and evidence indicates that the components of the motor unit discharge originate in the several fasciculi of which the unit is composed. Kisch & Schwarzschild (58) have encircled striated muscle with a surrounding ring of conducting material not impinging on the electrodes and have demonstrated resulting typical changes in the action potential records. This phenomenon has been used in the measurement of the conduction velocity in striated muscle.

The spike potential accompanying a single isometric twitch in striated muscle is followed by a slow negative after-potential which Bernhard & von Euler (59) have found to last about one second in the intact tibialis anterior muscle in the cat. The duration of the corresponding post-tetanic wave of negativity was shown to depend on the duration of the tetanus and might persist for as long as one minute. No correlation between after-potential and post-tetanic muscle tension was demonstrated.

Consideration of the action potential phenomena associated with cardiac muscle would lead to a consideration of the whole field of electrocardiography and is obviously beyond the scope of this review.

Clinically the study of the action potentials of skeletal muscle have been given the name "electromyography" and the use of the electromyogram as an aid to diagnosis is relatively common. The recent review by Weddell (60) covers the applications of this technique to the practice of clinical medicine. Ruesch & Finesinger (61) report that electromyographic measurements correlate well with subjective reports of muscular relaxation. Jacobson & Kraft (62) have made electromyograms from the right quadriceps femoris muscle in one hundred subjects engaged in silent reading under controlled conditions and it is planned that the composite curves obtained may serve as a standard for future investiga-

tions under similar conditions. Abnormalities of the electromyogram have been reported in cases showing localized tetanus (63), congenital myotonia (64), myasthenia gravis and progressive muscular atrophy (65), sciatica (66), and infectious polyneuritis (67). Fibrillary action potentials result in the typical electromyogram of denervated muscle and will be considered under this head later in the review.

As mentioned above, the electrical excitation of muscle may be made to elicit a group of phenomena demonstrating various electrical properties of this tissue. A number of workers report chronaximetric determinations of interest which have not been reported by previous reviewers. The chronaxie of muscle tissue has been measured in man before and after exercise (68), immediately after motor nerve section (69), in infants (70), in old age (71), during alcoholic narcosis (72), and during hypnotic sleep (73). There is a general tendency, especially in North America, to deprecate the value of measuring the parameters of excitation of excitable tissues. This is unfortunate as the rheobase, chronaxie, and time factor of accommodation can be determined with a considerable degree of precision and, if a large body of data were available giving these values as measured in a variety of pathological conditions, they might be found to have real diagnostic utility. It is true that several decades ago, notably in France, the measurement of chronaxie was a common clinical procedure. However, much of this data is of very little use in retrospect as chronaximetric measurements on muscle were and, in many cases, still are made in such a manner that it is impossible to tell whether the measurement is being made on the motor nerve fibre, the myoneural junction, or the muscle fibre. Even with modern equipment it is sometimes difficult to make this differentiation.

Rosenblueth & Acheson (74) have shown that the threshold of striated muscle to electrical stimulation is independent of the interelectrode distance and of the angle between the stimulating electrodes and the muscle fibres. In this respect muscle tissue apparently differs from nerve tissue and as a consequence the measurement of excitability constants should be simpler in the muscle than in nerve. Pollock & Finkelman (75) have shown that the gastrocnemius muscle, when stimulated electrically, becomes more negative at the proximal and more positive at the distal end. Injury to the muscle produces bizarre changes in the orientation

of these gross potentials which are unexplained and cannot be detailed here. Croisier (76) has analyzed the response of the crural triceps of the *Rana temporaria* to various types of electrical stimulation. He has shown that only low frequency stimulation elicits a sustained contraction. Stimulation at the middle and high frequencies results in only a transitory contractile effort on the part of the muscle. The reflex mechanism associated with these phenomena has been the subject of further investigation.

The use of electrical excitation for the diagnosis and treatment of a variety of pathological conditions involving muscle tissue encountered in clinical practice has been the subject of a number of recent reviews. Licht (77) outlines American practice and von Schwerin (78) has provided an account of European methods in this field of applied muscle biophysics.

The Physiology of the Myoneural Junction

The myoneural or neuromuscular junction is generally considered to consist of three parts: specialized nervous tissue supplied by the motor nerve fibre endings, specialized muscular tissue supplied by or more properly considered as part of the muscle fibre, and an intermediary tissue which is neither nerve nor muscle. This intermediary tissue, sometimes called the motor end-plate, is considered by some histologists to be the only differentiated tissue of the junction, to be indeed the myoneural junction itself. The work of Cuajunco (79) supports this view and indicates that the human motor end-plate is formed from the muscle sarcolemma at the time when the neurofibrils penetrate this membrane.

Kuffler (80) and Steiman (81) have studied neuromuscular transmission in the isolated nerve-muscle fibre preparation and the latter has been able to make observations in which a single nerve fibre has been excited to produce activity in the group of muscle fibres involved in the single motor unit. The neuromuscular junction was found to react in an all-or-none manner to fatigue and it was found that transmission fatigue and contraction fatigue were quite independent phenomena. Eccles (82) has demonstrated the similarity between the end-plate potential of a curarized muscle and the potential observed at a nerve synapse during the transmission of a nerve impulse. Extensive investigation of the curarized myoneural apparatus has been carried out by Belitzky (83) who has shown that the myoneural apparatus loses the ability to

conduct impulses in the sequence of increasing frequencies. Thus at first, conduction of a single impulse fails to take place, then that of a slow rhythm, and finally the conduction of impulses of higher frequencies (fifty to one hundred per second) is seen.

Kuffler (84) has studied the effect of calcium on the myoneural junction and shown that an excess of ionized calcium gradually blocks transmission at this point presumably by lowering the electrical excitability of the muscle fibre adjacent to the end-plate. Reduction of the ionized calcium to approximately one quarter of the concentration normally present results in a gradual increase of excitability at the myoneural junction. This increase ends in the repetitive response of the junction tissue and the muscle cell to a single nerve impulse impinging on the junction.

The motor unit offers a convenient preparation for the study of neurohumoral activity and has been used widely for this purpose. A number of workers have confirmed the generally-accepted view that the transmission of the nerve impulse from the muscle end-plate to the muscle fibre is humoral in nature and that the mediation is by acetylcholine or some acetylcholine-like substance (85, 86). The removal of acetylcholine has been studied (87, 88) and the function of cholinesterase, the enzyme responsible for this activity, has been investigated. Mendel & Hawkins (88) have obtained cholinesterase in a purified form. They have shown that the injection of this material into rats partially or totally abolished the direct light reflex activity of the sphincter pupillae and conclude that "the integrity of the reflex depends on the presence of acetylcholine at some point or points in the pathway of the nerve impulse." Potassium (89, 90) and adrenal cortical hormones (91) have been shown to be essential to the normal impulse transmission across the myoneural junction although the manner in which these substances are involved in the neurohumoral transmission is not understood.

Bülbring & Burn (92) have shown that the well-known potentiating effect of prostigmine on myoneural transmission is itself potentiated by epinephrine if the contraction rate is slow (four to six times per minute) but is decreased by this drug if the contraction rate is rapid (fifteen to thirty-five times per minute). Ephedrine has no direct effect on the prostigmine effect but enhances the modification of the prostigmine effect by epinephrine. Szepsenwol (93) has found that heart muscle cultivated in sym-

biosis with skeletal or smooth muscle rapidly becomes paralyzed and has been able to show that this paralysis is due to acetylcholine or an acetylcholine-like substance which is released from the skeletal and smooth muscle. This suggests the direct production of the neurohumor by muscle tissue.

The effect of various anesthetic agents on the neurohumoral transmission at the myoneural junction has been studied (94, 95). In low concentrations chloroform and ether have been found to increase the excitability of muscle by inhibiting the destruction of acetylcholine by cholinesterase. In larger doses chloroform, ether, cyclopropane, and sodium pentothal have a curare-like action and decrease the excitability of a muscle through its motor nerve or in response to injected acetylcholine.

The Physiology of Denervated Muscle

Many types of nerve fibres connect with skeletal muscle fibres and their associated structures in the intact muscle but it is probable that only the motor nerve fibres, axons of the lower motor neuron, are responsible for the control of the activity of the muscle fibres. A skeletal muscle fibre is said to be denervated when it is deprived of its lower motor neuron. When thus deprived muscle tissue undergoes typical changes which have been grouped under the term "degeneration of denervation." The principal phenomena associated with this degeneration are four in number: atrophy, fibrillation, changes in chemical excitability, and changes in electrical excitability. We will consider recent additions to the knowledge with respect to each one of these phenomena in order.

Atrophy or "wasting" is the most marked physical change which follows the motor denervation of skeletal muscle. This phenomenon has been observed since antiquity but even today we have no precise evaluation of the rate of atrophy in human skeletal muscle following its denervation. This information is available, however, for the muscles of several species of experimental animals, the most widely used of which is the white rat (96). Hines and co-workers (97) have made a comparative study of muscle atrophies caused by denervation and by acute inanition in the albino rat. No evidence was found that prolonged acute inanition resulted in functional denervation of skeletal muscle. Nerve stimulation elicited the same amount of tension relative to that from direct activation in both fasted and well nourished

animals. Cicardo & Gurevich (98) have investigated the changes in inorganic salt content induced by denervation and confirm the great body of work done by Hines and his collaborators in the conclusion that most, if not all, of the observed changes can be accounted for by the proportional decrease in active muscle tissue and increase in connective tissue which is brought about by motor denervation. Altschul (99) has made an interesting study of the nature of the atrophy resulting from the denervation of skeletal muscle. He describes the metaplasia of muscle fibres into connective tissue and the development of subsarcolemmal nuclei into fibroblasts or cellular elements of similar morphological characteristics.

Some days after the denervation of a skeletal muscle a fine random twitching develops over the surface of this muscle. In the human subject this twitching, or fibrillation as it is called, can be seen through the skin as a delicate "rippling" movement. Fibrillary activity is never sufficiently strong or adequately coordinated to result in overt muscular contraction. It is accompanied by electrical action currents and the presence of fibrillation can frequently be detected by recording these currents even when the movement is not sufficiently intense to be seen through the skin. Weddell, Feinstein & Pattle (100, 101) have reported on the extensive use of such electromyography as an aid to the clinical diagnosis of denervation. They find the differentiation of the normal muscle action potential from the fibrillary action potential a simple matter and can even diagnose partial denervation on the basis of a record in which the two types of activity co-exist. They find the onset of fibrillation to be extremely variable and to be inversely proportional to the size, that is to the metabolic rate, of the animal concerned. In the mouse, fibrillation commences in three and one half days after nerve section; in the rat four and one half days; in the rabbit six days; in the monkey eight days; and in man some eighteen days. Other authors have quoted figures considerably lower than these for the rat and for man. The underlying cause of fibrillary activity is not known although a number of investigators have suggested that it occurs as a result of the hypersensitivity of denervated muscle to acetylcholine, potassium, or both, and there is some evidence in favour of this view (102). However, Reid (103) has shown that fibrillation is unaffected by doses of curare which reduce the sensitivity of the denervated

muscle to acetylcholine. On the other hand, novocaine, usually considered to be curare-like in its action on muscle, stops the fibrillation of denervated muscle.

Lazere, Thomson & Hines (104) have shown that the gastrocnemius muscles of adult albino rats following denervation, immobilization by cast, or tenotomy showed a reduction in glycogen concentration. The fall in glycogen concentration and its subsequent recovery with reinnervation coincides in time with the appearance and disappearance of fibrillary activity in the case of denervated muscle. However, the fact that the phenomenon is seen in muscles showing atrophy without denervation, added to the observation that denervated muscles in animals treated with quinidine to prevent fibrillary activity still show the fall in glycogen, leads to the belief that these two phenomena are not related. It is suggested that the absence of tension development in the atrophic muscle might result in insufficient energy levels for the coupled reactions which might be required for glycogen synthesis.

Normal skeletal muscle is relatively insensitive to intra-arterially injected acetylcholine while denervated muscle is thrown into a prolonged contraction when exposed to this drug. Denervated muscle shows a similar but less striking increase in sensitivity to injected potassium. The mechanism underlying these changes in chemical excitability is not known. Kuffler (105) has investigated the specific excitability of the end-plate region in normal and denervated muscles and concludes that the hypersensitivity to acetylcholine and potassium is limited to the myoneural junction region and is not a property of the muscle fibre as a whole. On the other hand, Lyman (106) finds that denervated muscle is more permeable to potassium (radioactive to facilitate tracing) than is normal muscle and suggests that the sensitivity of denervated muscle to potassium may result from this change in the permeability characteristics of the muscle membrane. Reid (107) has shown that the adenyl content of skeletal muscle behaves like potassium after denervation.

Altschul (108) has carried out a further investigation on the effect of acetylcholine and prostigmine on denervated muscle. The chronic administration of these substances was found to have no effect on the course of the atrophy in the denervated muscles examined. From a consideration of the polarographic behaviour of the alkaloid obtained from *Chondodendron tomentosum* (d-tubo-

curarine) and other quaternary ammonium bases it seemed to McIntyre & King (109) that the rapid intra-arterial injection of this alkaloid should cause a contraction of denervated muscles in the same manner as acetylcholine. This was shown to be the case on the gastrocnemius muscles of dogs denervated ten days previous to the injection. Bender (110) has demonstrated an unexplained slow contraction produced in denervated skeletal muscle by the intravenous injection of certain barbiturates, notably sodium pentobarbital. The contraction appeared from sixteen to sixty seconds following the injection of sub-anesthetic doses of the drug and lasted for a minute or longer. It is thought that the barbiturate probably produces a release of acetylcholine from some other tissue in the body and that it is this substance which produces the contraction.

The changes in the electrical excitability of skeletal muscle induced by denervation have, in the past, been grouped under the term "reaction of degeneration." A great many phenomena have been collected under this heading but probably the only ones which should rightfully be included are the altered responses to galvanic and faradic excitation. In normal muscle galvanic current elicits a twitch when the current flow is started and another twitch when the flow is stopped; in denervated muscle galvanic current elicits a poorly-maintained tetanus. In normal muscle faradic stimulation elicits a tetanus; in denervated muscle faradic stimulation elicits little or no response. The value of electrodiagnostic procedures as applied to muscle has been emphasized recently (111) and the need for the introduction of more precise procedures into clinical practice has been stressed (112, 113). Pollock and his co-workers (114, 115) have shown that electrodiagnosis by means of progressively rising currents of long duration yields more precise information and at an earlier date when applied to denervated muscle than does the old crude comparison of excitation thresholds for galvanic and faradic stimulation. More recently he (116) has made use of an old observation made by Adrian and diagnosed the reinnervation of a denervated muscle on the basis of the appearance of a discontinuity in the strength-duration curve for the muscle. By combining the results of stimulation by progressively rising currents of long duration with a determination of strength-duration curve one may differentiate degenerating, recovering, and partial injuries in a manner not possi-

ble with the older procedures. Doupe (117) has shown that denervated muscle responds to galvanic or slowly rising exciting currents with a tetanic contraction because this tissue characteristically responds repetitively to any exciting current.

It is interesting to speculate on the genesis of the various phenomena comprising "degeneration of denervation" as seen in skeletal muscle. The four salient phenomena associated with the degenerative process are probably interrelated. At one time it was thought that the atrophy associated with denervation might be an over-work phenomenon associated with the fibrillary activity. There is now good evidence, based on several unrelated lines of experimental approach, that these phenomena are in no way related; the atrophy is certainly not the result of fibrillary activity (118, 119). It has been suggested that the atrophy is due to deficient circulation to the muscle and that the beneficial effect of electrical stimulation, which will be outlined immediately, is simply the result of the muscular contraction expressing the stagnated blood from the veins and venules in the muscle tissue (120).

The only effective treatment for denervated muscle is the reinnervation of that tissue. Any other treatment simply aims at keeping the muscle tissue in as good condition as possible pending its reinnervation. Gutmann (121) has carried out a large series of experiments on rabbits in which the peroneal nerve was crushed and observations on the recovery of muscle function made. Hines and co-workers (122) have carried out a similar series of experiments on albino rats in which the recovery of the gastrocnemius muscles was followed. Both sets of experiments were designed to furnish standards for further experiments on procedures designed to modify the return of motor function. Hines and his group have shown that neuromuscular atrophy and degeneration is in no way affected by vitamin E (123), biotin (124), or the vitamin-B complex (125) in the diets of the experimental animals. Soskin & Levine (126) have found that muscular atrophy following nerve section in monkeys can be significantly inhibited by treatment with atropine thus confirming their earlier work on rats. A number of groups, employing rats as their experimental animals, have failed to confirm this observation (127, 128, 119).

Immobilization of denervated muscles has been shown to retard recovery of function (129, 130) and indeed has been shown to produce an atrophy initially as severe as that due to denervation

in normally innervated muscles (118). Billig & van Harreveld (131) have interrupted the motor nerves serving partially paralyzed muscles with a view to producing a branching of the axons and a resulting increase in the number of fibres reaching the muscle. Beneficial results have been claimed. In the main it would appear that any procedure which delays the return of motor nerve fibres to a denervated muscle reduces the number of muscle fibres eventually reinnervated (132, 133), although the assessment of the final result is an extremely difficult matter even with the aid of muscle biopsies (134, 135).

Grodins, Osborne & Ivy (136) have reviewed the status of the use of electrical stimulation in the treatment of denervated muscle and, with reservations, have come to the conclusion that this is a useful procedure. Doupe and co-workers (137) treated denervated muscles in a number of clinical cases with rather limited electrical stimulation and found no beneficial effects. Gutmann & Guttmann (138), working on rabbits, found that exercise produced by galvanic stimulation of denervated muscles diminished the atrophy and, on reinnervation, resulted in a higher degree of motor recovery. A number of different types of exciting currents have been used in the treatment of denervated skeletal muscle in the albino rat (139). This work provides statistically significant evidence for the beneficial effect of electrically induced exercise on denervated muscle and shows that twenty-five cycle alternating (sinusoidal) current is more effective than sixty cycle, galvanic or faradic current. The effectiveness of the treatment increased with the number of treatments given daily up to the maximum of six and this relationship was linear over the range used. No sensible differences in result were obtained by varying the length of the individual treatment within the limits employed (one to five minutes). Hines & Wehrmacher (140) have carried out studies on the denervated gastrocnemius muscles of cats, guinea pigs, and albino rats and conclude that it is of the greatest importance to induce the development of tension in the denervated muscle and they point out that electrical stimulation is one effective and controllable means of bringing about this end.

Poliomyelitis

Anterior poliomyelitis or infantile paralysis results in a denervation of skeletal muscle which probably differs in no way from traumatic denervation but which many workers believe is accom-

panied by other bizarre changes in the skeletal muscle peculiar to this disease. Schwartz & Bouman (141, 142) find spasticity of the muscles in subjects suffering from infantile paralysis. This condition is said to be of a reflex nature and is not present in the completely paralyzed muscle. It is independent of muscle weakening and appears in agonist and antagonist muscles. Muscle spasm is relaxed temporarily by spinal anesthesia or block of the myoneural junction in acute and subacute poliomyelitis (143). Moldaver (144) claims that the spasm seen in the muscles of poliomyelitis is a complex and ill-defined phenomenon which does not lead to muscular degeneration.

Carey (145) finds morphological changes in the motor end-plates of muscles in monkeys infected with poliomyelitis virus. The disappearance of many end-plates resulting in denervation at the myoneural junction is described. Ephemeral appearance of masses of inclusion bodies, some of which are cross-striated, within and near the degenerating motor end-plate have been observed and were followed by a centripetal degeneration of the motor nerve fibre. Hitherto it has been believed that the denervation resulting from poliomyelitis always occurred at or adjacent to the anterior horn cell in the spinal cord. The histological work of Dublin and co-workers (146) on biopsy material taken from the skeletal muscles of patients suffering from poliomyelitis showed no process which could not be described as secondary to injury of the nerve cells in the spinal cord.

Electromyograms made from paralyzed muscles in cases of poliomyelitis and electrodiagnostic procedures carried out on such muscles demonstrate the findings which one would expect from denervated muscle (147, 148, 149) and which have been considered earlier in this review.

An adequate consideration of Sister Elizabeth Kenny's views on the pathological physiology of muscles affected by poliomyelitis is obviously not within the scope of this review. These views have been ably set forth by Pohl (150) and Knapp (151) with certain modifications which have been suggested by their own experience and the findings of Moldaver (152) and others who have taken an active interest in this vexing question.

Other Clinical Conditions Involving Skeletal Muscle

A great many such conditions exist but unfortunately very little is known about the abnormal physiology exhibited under

these circumstances. Northway (153) has considered the direct physical injury of muscle tissue. Such injuries are common even in the sports of peace-time and probably result in a permanent degradation of muscle power as ruptured muscle cells are not repaired but are replaced by connective tissue. The spontaneous activity of part of a muscle, called fasciculation by clinicians, is a phenomenon seen in a variety of pathological conditions and has been shown (154) to be abolished by curare and is thus thought to originate in the region of the myoneural junction. Harrison & Bigelow (155) have shown that the effects of analgesics upon visceral pain, such as that resulting from the contraction of ischemic skeletal muscle, are similar to those on superficial or cutaneous pain. Goetz (156) has described a new ergograph designed to facilitate the clinical investigation of muscle power particularly in patients suffering from intermittent claudication. Pollock & Brooks (157) describe an apparatus designed to facilitate the accurate evaluation of muscle power and the range of joint movements produced by muscle contraction. Fetterman (158) outlines two other tests designed to facilitate the bedside evaluation of muscle power. The appearance of all these tests, crude as many of them are, gives ample evidence of the interest being shown by the clinicians in muscle biophysics.

Fiertz (159) draws attention to the value of electrotherapy as applied to cases of facial spasm and vocal cord paralysis. Electrotherapy in connection with paralyzed muscles is a familiar procedure but the use of electrical stimulation to produce a sedative and soothing effect in muscle spasm is not so well known. Here the relaxing effect of anelectrotonus as observed about the anode of electrodes carrying a steady current is utilized. Electromyograms made on patients suffering from amyotrophic lateral sclerosis aid in the diagnosis, classification, and prognosis of cases and there appears to be a close correlation between the number of muscular fibrillations and the speed of progress of the disease (160). In this disease the fibrillary action potentials arise from muscle cell activity resulting from nerve impulses originating at or near the termination of the nerve fibres at the myoneural junction (161). Simplified ultraviolet photomicrography has revealed lesions of consistent character found in sections of muscles removed at biopsy from cases of progressive muscular dystrophy (162).

It has been shown that vitamin E plays an essential part in the

metabolism of skeletal muscle in all species of mammals that have been investigated (rats, rabbits, guinea pigs, hamsters, and mice) and in ducklings. Repeated trials have failed to indicate the importance of this vitamin in normal man or in man suffering from muscular disorders (163, 164).

It is well known now that myasthenia gravis is a disease characterized by certain abnormalities in the neurohumoral mechanism at the myoneural junction. Some relation to the thymus gland exists and thymus gland tumours are found in some cases whereas in others definite benefit results from thymectomy (165, 166) which is frequently carried out in spite of the danger attendant on the procedure (166). The blood of patients suffering from myasthenia gravis has been shown to contain some substance which interferes with neuromuscular transmission in the isolated nerve-muscle preparation of the frog (167). Further reports (168) claim that the production of acetylcholine from incubated frog's brain is significantly reduced in the presence of serum of patients with myasthenia gravis although other workers (169) have failed to confirm these findings. The underlying mechanism of the interference with neurohumoral transmission at the myoneural junction as seen in myasthenia gravis remains a mystry.

Concluding Remarks

The past two years have been disappointing in their yield of investigation of fundamental importance in the field of muscle physiology, especially muscle biophysics. This is natural at a time when the attention of most physiologists is directed to the solution of the immediate, practical problems facing people at war. Some compensation is furnished by the fact that there has been great acceleration in the application of laboratory procedures to the solution of clinical problems. This is particularly true in the fields of electromyography, electrodiagnosis, and the electrical treatment of civilian and service casualties suffering from the traumatic denervation of skeletal muscle. We trust that the collaboration between laboratory and clinic established in war-time will carry over into the years of peace.

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DEPARTMENTS OF PHYSIOLOGY AND PHYSIOLOGICAL HYGIENE
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DIGESTIVE SYSTEM[1]

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Secretion

Salivary glands.—The modal value for the so-called "resting" saliva in healthy young persons is 0.24 cc. per minute (1). When dehydration reached 8 per cent in humans, under the conditions of high temperature and low relative humidity prevailing in the desert, the secretion of saliva in response to chewing of paraffin approached zero. Oral administration of pilocarpine stimulated the flow of saliva in a dehydrated man but did not alleviate thirst (2).

About three weeks after tying of the pancreatic duct alone or in conjunction with the accessory pancreatic duct, the amylolytic activity of dog's mixed saliva suddenly increased. The increase persisted for seventy-eight days (duration of the longest experiment). No change was found in the diastatic power of the blood (3). The concentration of uranium in the human parotid gland was $1.33.10^{-8}$ gm. uranium per gram of gland (4). An increased concentration of iodine in human saliva was noted after oral administration of potassium iodide, iodine dissolved in poppy seed oil, or ethyldiiodobrassidate (5).

Faradization of the peripheral end of the chorda tympani in dogs increased the respiratory movements and the motility of the small intestine, and when physostigmine had been given previously also produced a transitory fall of blood pressure. It was concluded that the chorda tympani liberates two substances: one of the nature of acetylcholine, the other of unknown nature but resistant to cholinesterase (6).

A copious salivary secretion was elicited from the homolateral submaxillary and parotid glands in a cat in which the medulla was stimulated with a weak induction current (7).

Gastric glands.—The theory was formulated that the production of pyloric hormone (gastrin) is essential for the secretory activity of the vagus nerves (8). If the pyloric region of the stomach in cats or dogs was disconnected from the rest of the organ by a

[1] This review covers the literature to July 1944.

ligature, or deprived of its arterial blood supply, or resected, or its function depressed by cocainization, the gastric secretion evoked by faradization of the vagi stopped or was greatly diminished. Intravenous administration of an extract of pyloric mucosa (Komarov's "gastrin") restored the lost activity of the vagi. In cross-circulation experiments faradization of the vagi in a cat, in which the pyloric mucosa was cocainized, produced a secretory effect only when blood from another cat, subjected to vagal stimulation with the pyloric mucosa intact, was transfused into the first animal. Because in the hands of this experimenter gastrin produced a very insignificant effect, he concluded that the relations between the secretory effect of the vagi and gastrin are reciprocal. However, it was demonstrated that the vagus nerves alone, without the help of the pyloric hormone, are able to elicit a copious secretion of gastric juice (9). Removal of the mucous and submucous membranes of the pyloric region, or resection of the pyloric part *in toto*, inhibited the gastric secretion in response to vagal faradization in dogs for only one to two hours, after which time the secretion returned to the preoperative level or even exceeded it.

Vasodepressor-free liver extract evoked a greater gastric secretion from a vagotomized entire-stomach pouch in the dog when perfused through the pouch than when administered intravenously. It was concluded that this secretagogue acts either by stimulating the production of a gastric hormone or by stimulating the glands directly after it is absorbed in an altered form (10). The pepsin concentration and output in the gastric juice secreted by a transplanted pouch, when a vagally denervated pouch of the remainder of the dog's stomach was perfused with histamine-free liver extract, were of the same low order of magnitude as in the case of juice evoked by histamine stimulation (11).

The secretory function of the gastric glands in dogs proved to be extremely resistant to a diminished blood supply (12, 13).

The variations in the osmotic pressure of gastric juice secreted by a Heidenhain pouch in the dog in response to histamine or pilocarpine were interpreted as indicating the presence in the juice of at least three secretory components: an approximately pure hydrochloric acid, a neutralizing or buffering component probably similar in composition to blood plasma, and a neutral diluting component (14).

A major part of the mucus present in the gastric juice secreted

by different gastric pouches in dogs in response to pilocarpine was produced by mechanical factors (15). Pilocarpine stimulates directly a copious flow of hydrochloric acid, water, and pepsin, and indirectly the discharge of mucus from the surface-epithelium cells by increasing the motility of the gastric mucosa (16).

Endoscopic examination of the gastric mucosa, when subjected to different types of stimulation, was performed in anesthetized dogs (17). Human gastric mucosa contains histamine or a histamine-like substance. The average activity of extracts of fundic mucosa was equivalent to 10.2 mg. histamine per kg. of mucosa, that of extracts of antral mucosa to 5.8 mg. (18). Five compounds of histamine with several amino acids were prepared. Before hydrolysis with hydrochloric acid the effect of these compounds on blood pressure was insignificant; after hydrolysis, when histamine was set free, it was very definite. Since histamine is present in the cells in an inactive form, these studies give an indication of how it may lose its pharmacological properties on entering into chemical combination with amino acids (19).

Gastric secretion is continuous in the rat. Histamine, when administered subcutaneously to anesthetized rats, has little if any effect on gastric secretion (20). Stimulation of gastric secretion by histamine in dogs was followed by a decrease in the magnitude of the potential. After reaching a new level the potential remained more or less constant while the rate of gastric secretion continued to increase (21).

Some preparations of secretin, e.g., Ivy's secretin I (SI), besides evoking pancreatic secretion, slightly increased the discharge of pepsin by the gastric glands in response to histamine in cats. It was possible to separate secretin from the pepsigogue substance by chemical treatment, though the latter substance was not isolated. Crystalline secretin was devoid of pepsigogue effect (22). Enterogastrone, administered parenterally or formed under the influence of fat in the intestine, diminished the volume of gastric secretion and the output of pepsin moderately (23). Gastric secretion is stimulated by bile when the latter is in the stomach but not when it is in the small intestine; however, when admixed to a protease solution and introduced into the intestine, it increases gastric secretion (24). It was observed that on introduction into the intestine hydrochloric acid (pH between 6.5 and 2.5) had a pepsigogue effect on the gastric secretion produced in dogs by feeding

or by insulin but not on the secretion evoked by histamine. If the pH of the acid was below 2.5, the secretion of pepsin as well as that of acid was depressed (25, 26).

Parathyreokrin, administered subcutaneously, diminished gastric secretion and motility in dogs. A preparation of the parathyroid glands lowered the gastric acidity in 50 per cent of cases in patients with hyperacidity (27). Parenteral administration of pituitrin or of "hypophysolysate" inhibited gastric secretion and increased the hunger contractions in dogs. In patients with hyperacidity the same substances lowered the gastric acidity and eliminated constipation in 50 per cent of cases (28).

Repeated injection of mecholyl produced an abundant secretion of acid gastric juice rich in pepsin, whereas a large single dose evoked a scanty secretion of low acidity but high peptic power. The pyloric portion of the stomach responded to mecholyl with a secretion of alkaline mucus devoid of pepsin (29). Caffeine does not elicit gastric secretion in dogs, but when introduced intravenously or directly into the stomach in cats it stimulates gastric secretion. Caffeine is a gastric stimulant in man, when administered intramuscularly or by mouth (30). Furthermore caffeine in a concentration of 20 to 40 mg. per 100 cc. of substrate *in vitro* does not influence the action of ptyalin, pancreatic amylase and lipase, and trypsin and pepsin. However, coffee extract enhanced the effect of salivary and pancreatic amylases, inhibited the action of lipase, and influenced the effect of pepsin and of trypsin (31). Sodium bicarbonate in 1.5 and 2 per cent solutions given three times daily in doses of 50 cc. by stomach tube to Cope-pouch dogs increased the gastric secretion during the hours immediately following a test-meal, and decreased it during the later hours (32). Neurine, as bromide, when administered intramuscularly in dogs, evokes a secretion of acid gastric juice. The threshold dose of neurine is 150 times greater than that of histamine (33). 929F does not inhibit the secretory response of the Heidenhain pouch to histamine in dogs, and inhibits the response of this pouch to mecholyl very little. It inhibits the secretory response of Pavlov, Heidenhain, and transplanted pouches to meals, and 1571F inhibits the response of the Pavlov pouch (34).

After intravenous administration of sodium sulfapyridine, sulfathiazole, and sulfadiazine to patients, these drugs appeared in the gastric secretion. Dogs which received sulfanilamide, sulfathi-

azole, sulfadiazine, succinylsulfathiazole, neoprontosil, and sodium sulfapyridine intravenously excreted these drugs with the gastric juice. The last-mentioned drug was also found in the pancreatic juice and the bile after intravenous administration (35). The gastric mucosa possesses a mechanism whereby iodide is excreted in concentrated form (36).

The effect of various detergents on peptic activity has been dealt with in a number of contributions (37 to 42). No rennin is present in the gastric juice of adult persons (43).

The response of the gastric glands in man to a caffeine test-meal during an airplane flight depended on the character of the flight. Gastric secretion was depressed and evacuation of the stomach delayed if the flight was smooth and at a uniform altitude (whether low—1800 to 2000 meters, or high—4300 meters). If the plane was subjected to frequent falls into air-pockets and the rate of flight consequently often varied, an increase in gastric secretion was noted. This last effect was coupled with manifestations of air-sickness (44).

Removal of about half the blood by bleeding greatly diminished the gastric secretion in Pavlov- and Heidenhain-pouch dogs. The secretion returned to normal in about two weeks (45).

Peptic ulcer.—Vascular spasm produced by intravenous administration of pitressin caused erosions and ulcers in the gastric mucosa in 37 per cent of dogs (46). Caffeine in a mixture of beeswax and mineral oil, administered intramuscularly over a period of time, produced bleeding erosions or ulcers chiefly in the stomach in 40 per cent of guinea pigs (47) and 50 per cent of cats (48). Certain chemical agents—calgen, hexylresorcinol, pinacol, and methylsalicylate—which increase the permeability of the gastrointestinal mucosa—facilitate the formation of ulcers by pepsin and hydrochloric acid (49). The best method of preventing the formation of jejunal ulcers in dogs treated with histamine-beeswax was by extensive gastric resection (50). Treatment of Mann-Williamson dogs with enterogastrone prevented ulceration; after one year's treatment they remained ulcer-free and responded normally to alcohol test-meals for two and one-half years (51).

Implantation of a jejunal pedicle graft in the stomach of normal dogs was more effective in lowering the acidity of the fasting, "histamine," and "alcohol" gastric secretions than a graft from any other part of the intestine (52). In dogs with the jejunal transplant

the pH of the gastric mucosa after histamine was higher than in normal animals (53). Introduction of 25 cc. of saline washings from an isolated jejunal loop for a ten minute period into the stomach of a dog depressed the secretory response of the stomach to histamine (54). Contrary to this it was stated elsewhere (55) that the "histamine" gastric secretion from a dog's total-stomach pouch was not inhibited by jejunal washings. The reversal secretory effect of histamine on a stomach grafted with a jejunal pedicle likewise could not be obtained.

Pancreatic gland.—The presence of peptone in the intestine produces changes in the acinar cells of the dog's pancreas similar to those observed after faradization of the vagi (56). The specific gravity and total nitrogen of dogs' pancreatic juice varied according to the stimulant with which pancreatic secretion was evoked (57). In dogs secretin (SI) and epinine produced pancreatic secretions poor in amylase, lipase, and trypsin, whereas prostigmine and sodium nitrate evoked secretions rich in all three enzymes. It was concluded that sympathomimetic amines acted directly on the acinous cells (58).

An adaptation of enzymes in the pancreatic tissue to dietary composition was observed in rats kept on a balanced diet (59).

The source of the alkali of the pancreatic juice is believed to be not the gland itself but the blood, since the alkali reserve of the pancreas in the cat after a copious secretion evoked by secretin does not differ from that of a resting gland. The potassium, sodium, and calcium contents of the cat's pancreas likewise do not change during profuse pancreatic secretion (60).

When given to depancreatized dogs maintained with insulin, even very large doses of lipocaic (equivalent to 100 gm. of raw pancreas) did not prevent either the development of fatty liver or a fall in blood cholesterol, phospholipids, or total fatty acids below preoperative levels (61). Preliminary feeding of raw pancreas for three to eight weeks to depancreatized dogs under insulin treatment did not lead to storage of the anti-fatty factor, and the normal content of lipids in such animals when pancreatic juice was afterwards administered could not be accounted for (62). Further results concerning lipocaic have been reported (63).

Bile and biliary tract.—A valuable study of the blood supply and innervation of the choledochoduodenal junction in the cat was carried out (64). The interdigestive discharge of bile in normal

subjects and patients is not a purely motor phenomenon but depends also on the rhythmicity of bile secretion (65).

Since, after severance of all the extrinsic nerves to the sphincter of Oddi in cats, the ganglionic cells and postganglionic fibers did not degenerate, the normal response to a meal of egg yolk is to be explained by the fact that the local nervous apparatus continued to respond to hormone-producing substance (66).

Three interesting papers (67, 68, 69) on cytological changes in the diurnal cycle of the mouse's liver and the effect of trypan blue upon that organ should be read in the original.

Several contributions (70 to 74) deal with the excretion of different substances along with the bile.

In ten out of twelve cholecystectomized dogs there was a rise in serum phosphatase. In one of the dogs the phosphatase content later returned to normal. Only four of the animals developed an increased retention of bromsulfalein (75).

Small intestine.—Sodium thiocyanate (1.5 gm.), given by stomach tube to dogs with transplanted intestinal segments or with fistulas of different parts of the intestine, increased the rate of intestinal secretion (76). A more accurate but rather complicated method for bioassay of enterocrinin in dogs has been suggested (77). A detailed procedure has been described for obtaining highly potent preparations of enterocrinin (78).

Raising of the basal metabolism to the hyperthyroid level by means of thyroxin in dogs with a Thiry-Vella fistula increased the volume of the jejunal secretion and the total production of mucoprotein and of all enzymes, except phosphatases. Thyroidectomy did not affect the rate of jejunal secretion (79).

A diminution in the volume and enzyme content of the intestinal secretion was observed in Thiry-fistula dogs during (but not after) an airplane flight, whether the altitude was low (500 to 800 meters) or high (4,200 meters). This effect was presumably due to changes in the speed and to the airplane falling into air-pockets (80).

Miscellanea.—The effects of morphine and other opium alkaloids (81) and of atropine (82) on gastrointestinal functions have been discussed. The role of psychodynamic factors in diseases of the gastrointestinal tract have been analyzed (83). Anatomical and functional changes in the gastrointestinal tract of patients suffering from sprue have been described (84).

Work on the mechanism of the secretory activity of the digestive glands has been reviewed (85, 86).

Motility

Swallowing.—The epiglottis does not remain upright during swallowing but turns over to act both as a chute for the food and a guard for the larynx (87). A new reflex involving swallowing has been described: an involuntary swallowing movement occurs when a subject, with eyes closed, suddenly immerses his head in cold water (88). Swallowing of amniotic fluid by the fetal monkey *in utero* increases in frequency as gestation progresses (89). Three types of muscular activity of the human esophagus were observed roentgenologically. A primary wave begins at the pharynx, a secondary wave begins in the region of the aortic arch, and a tertiary or localized contraction may occur which is not peristaltic in nature (90).

In man tactile sensibility extends only to the pharyngeoesophageal junction, but the esophagus is sensitive to heat and cold (91).

Gastric motility.—Rhythmic segmentation of the human stomach similar to that in the intestine has been described. The pyloric part was seen to contract completely even while the corpus remained relaxed. Antagonism between rugae formation and activity of the muscular layer seemed to exist (92). By means of the pyloric inductograph, the pyloric sphincter of the fasting dog was shown to exhibit as a rule rhythmic contractions at the rate of 4 to 6 per minute. The sphincter was open more than half the time. The frequency and magnitude of the pyloric contractions were slightly greater in fed animals, and quiescent periods were rare (93). Reflux of duodenal contents is prevented by contraction of both sphincter and antrum. Food or acid in the upper small intestine retards gastric evacuation by depressing gastric motility, and occurs even with simultaneous depression of the sphincter and bulb (94). The decreased gastric evacuation that occurs during emotional states was found to be due to depressed gastric motility and not to pylorospasm (95).

A definite decrease in gastric tone and peristalsis was found in many human subjects after subjection to motion tests. This decreased motor activity occurred five times as often in subjects who developed "motion sickness" than in those who did not, while the

incidence of pylorospasm was not correlated with "motion sickness" (96). In dogs susceptible to motion sickness all gastric movements of the fasting stomach were inhibited and continuation of swinging induced vomiting in five to fifteen minutes. After cessation of swinging most dogs exhibited special rhythmic contractions of the stomach associated with a lowered gastric tone, which were not affected by atropine nor induced by prostigmine. In two susceptible dogs bilateral labyrinthectomy abolished the motion sickness (97). Delayed gastric evacuation was found in a series of patients with duodenal ulcers (98).

Olive oil in the usual therapeutic dose had only slight over-all effects on gastric emptying: the unsplit oil at first hastened emptying but later the fatty acids inhibited it (99). The emptying rate of the rat's stomach decreased progressively as greater concentrations of glucose were fed (100). Water (500 to 1,000 cc.) taken with a meal had no effect on gastric emptying in man (101). No differences in gastric emptying were observed in children fed fresh, evaporated, or homogenized milk (102).

In unanesthetized dogs intravenous administration of extracts of urine from normal men and duodenal-ulcer patients inhibited gastric motility. It was concluded that the motility-inhibitory factor in human urine was not identical with the ulcer-preventing factor previously described (103).

In sixteen out of seventeen young men the gastric emptying times at the temperatures of 77°F. and 120°F. were decreased by 30 per cent (104). In women, no significant difference was found in the initial rates of gastric emptying in primigravidae and nulligravidae (105).

The effects of morphine on the stomach are potentiated by cholinergic drugs (106). The effects of barbiturates (107) and metrazole (108) were investigated. Intravenous administration of a casein hydrolysate caused less vomiting than did a mixture of ten crystalloid amino acids; the unnatural isometric forms of amino acids were believed to be responsible (109).

Intestinal motility.—In the avitaminosis of sprue, hypermotility and hypertonicity were manifested by the small intestine during the early stages of the deficiency but in the advanced stages hypomotility and dilatation with abnormal segmentation were present (110).

An oxygen partial pressure of 94 mm. Hg (equivalent to an alti-

tude of 14,000 feet) did not affect peristalsis of the small intestine in mice but partial pressures below this decreased peristalsis. In dogs (111) intestinal activity was not affected by oxygen partial pressures as low as 43 mm. Hg (corresponding to 32,000 feet). In dogs subjected to hemorrhage equivalent to 20 per cent of the calculated blood volume, a charcoal gum-acacia meal traversed 73 per cent of the gut length as compared with 54 per cent in control animals (112). In dogs with chronic Biebl loops intestinal tonus and peristalsis were not affected by initial blood loss of 20 cc. per kg. Tonus fell sharply on further exsanguination when blood pressure was reduced to 84 to 54 mm. Hg, while peristalsis disappeared at about 40 mm. Hg. During reinfusion of the blood previously removed, tonus returned at 40 to 50 mm. and peristalsis at 50 to 75 mm. Little change in motor activity occurred in adrenalectomized dogs when blood pressure fell as low as 30 to 40 mm. As hypotension increased, peristalsis increased and became abnormal. Nephrectomized dogs required lower blood pressures to depress motility than did intact dogs (113).

In fasting dogs, 20 cc. of 10 per cent dextrose given intravenously lowered intestinal motor activity but as much as 40 cc. of 40 per cent dextrose was required to produce distinct depression when the intestine was denervated (114). Duodenal hypermotility of short duration was produced in unanesthetized dogs by intravenous injection of a commercial casein digest. A long period of inhibition sometimes followed the hypermotility (115).

In trained dogs with chronic intestinal fistulas and loops, various anesthetics, except spinal, either had no effect or else depressed both tonus and motility. Spinal anesthesia increased intestinal activity. Morphine first produced a transitory increase in motor activity, followed by extensive depression, the depression being greater than that produced by any other anesthetic studied (116). The inhibition of intestinal motility and tone produced by local application of topical anesthetic drugs was believed not to be due to reflexes along long arcs or to vascular effects but to local action on sensory receptors with curtailment of local motor reflexes (117).

Ergotamine and prostigmine increased the rate of passage of charcoal along the small intestine of unanesthetized dogs by 27 and 38 per cent respectively, while ephedrine and atropine decreased motility by 35 and 36 per cent, and cocaine had no effect

(118). Atropine and trasentine were found to be the most effective intestinal antispasmodics, while trasentine and nitroglycerine were superior to atropine, opium-belladonna, and amylnitrite in the presence of spasm of the sphincter of Oddi (119). A comparative study of the effects of different drugs on the contraction waves of the jejunoileum in man was made (120). Amidopyrine (pyramidon, aminopyridine) produced relaxation of isolated intestinal loops as well as of intestinal muscle strips even in the presence of pilocarpine. The effect was presumably local, since intravenous administration of the drug had either a transient inhibitory or no inhibitory effect (121).

$Ca(H_2PO_4)_2$ decreased the tonus and peristalsis of isolated intestinal strips more effectively than either $CaHPO_4$ or $Ca_3(PO_4)_2$ (122). Amphetamine and similar sympathomimetic drugs, whose inhibitory action on intestinal strips develops slowly, probably act directly on the musculature and not through sympathetic nerve endings or specific receptors (123). Arginine and histidine are capable of decreasing or abolishing the effect of histamine on intestinal strips of the guinea pig. These amino acids did not abolish the effect of acetylcholine but sometimes decreased it (124). Quinine first increased and then decreased the tone of the rabbit's small intestine. Absence of oxygen enhanced the quinine effect while oxygen and epinephrine antagonized it (125).

Large bowel.—Radiological observations on the human colon and cecum were made and the motor activities classified according to distinct patterns (126, 127). Diminution in the height and frequency of contraction of the longitudinal muscle of the dog's colon was observed in the majority of dogs after a blood loss equivalent to 2.2 per cent of the body weight but an occasional animal was highly resistant to even more severe hemorrhage (128). A partial pressure of oxygen of 110 to 94 mm. Hg (equivalent to 10,000 to 14,000 feet altitude) inhibited both the circular and the longitudinal muscle of the dog's colon (129). Above altitudes of 20,000 feet the colon of the fasted dog increased progressively in size. When a given altitude was reached and maintained, colon size tended to decrease again owing to the expulsion of gas via the rectum rather than to absorption by the mucosa. Below 27,000 feet peristaltic activity was noted to be more marked than at higher altitudes (130). It was also found that following injection of room air into the colon there occurred variations in intraluminal

pressures of 4 to 35 cm. water (131). Increased pressures corresponded to marked contractions of the colon. Both pressure and motility were decreased and colon size increased by intravenous administration of an antispasmodic drug.

Innervation.—The cerebral cortex influences gastrointestinal motility in dogs by means of transient cortical impulses caused by sudden "conditioned stimuli" and prolonged cortical impulses caused by prolonged exposure to "food surroundings." The "short" conditioned stimuli result in cortical stimuli which initiate gastric and intestinal motility, the latent period usually being less than one to three minutes and the duration of effect from thirty seconds to five minutes (132).

Electrical stimulation of the cat's midbrain in the neighborhood of the septum pellucidum and the stria terminalis resulted in defecation and micturition (133). Stimulation of points in the elongated region of the ventral nucleus of the thalamus, as well as of those near the medial edge of the pes pedunculi cerebri and in the septum, hypothalamus, and corpus collosum, evoked coordinated movements of licking and chewing (134). The midbrain is considered as an organ of coordination where certain functions are combined to result in a single act and also from where impulses may be transmitted to higher brain centers (135).

Intestinointestinal inhibitory reflex connections are believed to be effected in the prevertebral ganglia. The inhibitory reflex was still present in the large intestine following degeneration of the visceral afferents from the colon via the inferior mesenteric plexus and the preganglionic fibers of spinal origin. Following decentralization of the celiac and inferior mesenteric ganglia, distention of the ileum or stimulation of the mesenteric nerves as well as distention of the transected colon or stimulation of its nerves resulted in inhibition of motility in the respective proximal segments (136).

In unanesthetized dogs with Thiry fistulas of the jejunum the motor action of physostigmine and prostigmine was the same on the completely extrinsically denervated loop as on the innervated loop (137).

A substance appearing in dog's blood during both digestive activity and hunger contractions has been identified as acetylcholine (138). The highest concentration of acetylcholine was found to occur in the upper jejunum and the lowest in the esopha-

gus and colon. The muscularis of a given region always contained more acetylcholine than the mucosa (139). The acetylcholine content of the myenteric plexus in the rabbit and the guinea pig is higher than that of any other tissue. It is suggested that there is a relationship between the great resistance of the intestine to anoxia and the high content of acetylcholine in the intestinal plexuses (140).

Both electrical stimulation of stomach strips and application of acetylcholine caused the liberation of potassium. This effect was increased by physostigmine but prevented by atropine (141). Smaller doses of potassium chloride were found to stimulate rhythmic activity of the circular muscle of rabbit intestine and larger doses increased the tone. The potassium acted directly on the muscle. Hypertonic sodium chloride caused outbursts of rhythmic activity which were paralyzed by nicotine but not by atropine in doses effective against physostigmine. Hypertonic lactose and sucrose solutions acted similarly. The effect of hypertonic solutions was believed to be through Auerbach's plexus (142). Potassium chloride renders the turtle stomach less irritable to subsequent vagus stimulation. The potassium effect on this vagus threshold was antagonized by cardiac glucosides (143).

Visceral atrophy and spastic contractions of the small intestine were observed in chronically adrenalectomized rabbits. The activity of the longitudinal muscle, as seen in strips, was normal but the circular muscle showed powerful spasmodic rhythmic contractions. Drugs known to act on Auerbach's plexus failed to act in the adrenal-deficient animal but the effect of drugs acting directly on the muscle was normal. Cortical extracts did not restore functions to normal (144).

Miscellanea.—The blood flow through loops of small intestine immersed in low-temperature baths increased when the temperature was lowered and decreased when it was raised. Section of the mesenteric nerves and cocainization of the loops did not affect the responses (145).

Injury to the mucosa of the stomach produces a positive (rather than a negative) injury potential, which is directed inward from the mucosa (146). The electric potentials from the intact human small intestine, or from the small intestine previously exteriorized, were found to be similar to those obtained from isolated muscle preparations and could be correlated with intestinal motor activity (147).

Absorption

Carbohydrates.—Establishment of a conditioned reflex absorption of sugar from the intestine of the dog was reported (148).

The rate of glucose absorption by the rat increased significantly with the concentrations fed. Younger animals absorbed concentrated solutions more slowly than older ones, while absorption was slower after a 48-hour than after a 24-hour fast. In anesthetized rats little or no glucose was absorbed from the stomach (100). In dogs with jejunal and ileal fistulas glucose and glycine absorption from the jejunum was greatly delayed as the result of deprivation of the whole vitamin-B complex. The normal absorption rate was restored by administration of vitamin-B complex either by mouth or by vein (149). Glucose and 3-glucose methyl ether were absorbed at equal rates from an intestinal loop of the anesthetized rat, but 2-glucose methyl ether, 5-glucose methyl ether, and 6-glucose methyl ether were absorbed more slowly (150).

In 65 people, ranging in age from 13 to 108 years, the maximum rate of intestinal absorption of galactose was found to occur between 18 and 24 years (151). In the rat riboflavine deficiency had no effect on galactose absorption but marked reduction occurred in both thiamine- and pyridoxine-deficiency states (152).

Enterostomized dogs maintained exclusively on a diet of whole bread (without crust) ultimately developed a severe deficiency characterized by a 40 to 60 per cent decrease in the rate of carbohydrate digestion and absorption. Calcium pentothenate had an almost immediate effect in restoring these functions to normal but pyridoxine and inositol were ineffective (153).

There was found to be a slight but unequivocal preferential absorption of the levo form from both the small intestine and the colon of the decerebrate cat after administration of *dl*-mandelic acid. Absorption still occurred but the selectivity was absent from the intestine of cats under ether or chloroform anesthesia or cats recently killed, and *in vitro* from isolated intestinal loops (154).

Proteins.—Horse albumin, globulin, and serum were placed in the duodenum of guinea pigs previously sensitized by the corresponding protein. These native proteins passed through the intestinal epithelium, since fifteen to thirty minutes later the uterus was found to be desensitized (155). Absorption of amino acids

from the gastrointestinal tract of the chick varied inversely to the molal volume of the amino acid (156).

Lipid compounds.—Olive oil can be lipolyzed by lipase alone but is not emulsified. In the pH range 6.0 to 8.5 the fatty acid was found to supply the necessary stabilizing charge at the higher limits of this pH range, while in the more acid medium the fatty acid bile-salt complex provides the stabilizing charge when ionization of the fatty acids is depressed (157, 158). Further evidence is presented from the same laboratory that lipolysis is not an essential step in fat absorption but that it determines the route and destination of the fatty material. While the feeding of neutral fat results in systemic lipemia, milkiness of the intestinal lacteals, and deposition of the fat in fat depots, the feeding of excessive amounts of lipase with the neutral fat results in portal but not in systemic lipemia and in deposition of fat in the liver rather than in fat depots (159).

Volatile fatty acids are the chief nongaseous products of bacterial composition of cellulose in the sheep rumen. Absorption of these fatty acids occurs in the stomach and is not delayed until the small intestine is reached. In the rabbit these fatty acids are absorbed about three times as rapidly from the cecum as from the small intestine (160, 161). The presence of a normal functioning gastric mucosa is necessary for the proper absorption of fat, since in cases of gastrointestinal disease abnormal fat absorption occurred only in the totally gastrectomized patient and the patient with atrophic gastritis (162).

Subjection of rats to a reduced pressure of 25.4 mm. Hg was found to lower significantly the amount of fat absorbed (163).

The role of the adrenal cortex in fat absorption is still uncertain. Short-chain fatty acids were absorbed in the adrenalectomized rat as rapidly as in the normal rat but intestinal absorption of the longer chain fatty acids was distinctly reduced (164). Other workers (165) found that in seven patients with well-developed Addison's disease administration of adrenal cortex hormone, while improving the patient's condition, had no effect on fat absorption. Although bile plays an important role in the absorption of fat, fat-soluble vitamins, and cholesterol, various steroids are readily absorbed from the rat intestine even in the absence of bile (166). In immature female rats the intestinal absorption rates of

different steroid hormones and hormone derivatives differed markedly (167).

Quinine reduced absorption of fat by 23 per cent and that of fatty acids by 9 per cent when it was introduced with the fat or fatty acids into a segregated portion of the ileum. Given by vein quinine had no effect. Presumably quinine decreased the rate of hydrolysis of fat but had no effect on its resynthesis in the mucosa from fatty acids (168). An interesting observation possibly related to fat absorption was made (169). The lipemia resulting from feeding of fat to dogs was rapidly abolished by intravenous administration of heparin. No reaction occurred *in vitro* when heparin was added to lipemic plasma.

Vitamins.—Although the vitamin intake may be adequate, vitamin deficiencies may develop through interference with intestinal absorption. In chicks four times as much vitamin D was required when sulfur was included in the diet as when sulfur was absent. Sulfur apparently did not influence the absorption of carotene or riboflavine (170).

In children a low level of vitamin-A absorption has been associated with poor fat absorption (171), but in the rat no correlation exists between the rates of absorption of neutral fat and vitamin A, the latter being absorbed in proportion to the concentration administered (172). Vitamin-A absorption in the rat occurred maximally at the border between the upper and middle thirds of the small intestine. Even after huge doses were administered, all the vitamin had disappeared from the lumen at levels below the duodenum. Although maximum fat absorption also occurred in the same region, fat was demonstrable in the lumen throughout the length of the small intestine. Simultaneous administration of vitamin E did not influence vitamin-A absorption but atropine greatly diminished it (173). Although in man atropine delayed the absorption of vitamin A, it was uncertain whether this was in consequence of the decreased motor activity of the intestine or the inhibition of the pancreatic and biliary secretions (174).

Like vitamin A, carotene is reported to be absorbed in proportion to the dose. However, unlike vitamin A, there appears to be a considerable correlation between the amounts of fat and carotene absorbed (175). The availability for absorption of vitamin A and carotene is greatly increased by the presence of alpha-, beta-, or gamma-tocopherol. The sparing action of the tocopherols is be-

lieved to be due to repression of oxidation in the gastrointestinal tract (176).

Minerals.—Active absorption of radioactive iron from the stomach occurred. The iron normally absorbed by the dog was increased five to fifteen times in chronic anemia due to blood loss. No significant increase in absorption occurred following sudden production of anemia. Anoxemia of 50 per cent normal oxygen concentration for forty-eight hours also did not increase iron absorption. The concept of "physiologic saturation" of the gastrointestinal mucosa with iron may explain the acceptance or refusal of iron. Saturation may take one or two hours but desaturation takes days (177, 178). Other workers (179) also advance the theory that iron absorption is regulated by the amount of storage iron in gastrointestinal tissues.

In studying absorption and excretion of iron in young women, better than 50 per cent of a daily iron supplement of 126 mg. in the form of ferrous sulfate was found to be absorbed. The conclusion that the body has no ability to control its depots of iron by regulating either its excretion or its absorption is seemingly in disagreement with that mentioned above (180). Iron is absorbed by the capillary vessels of the intestine and apparently not by the lymphatics (181).

During liver treatment of the pernicious anemia patient, serum iron falls because of increased requirements for iron, but iron absorption from the intestine is not improved (182). Iron absorption in normal and anemic patients was in proportion to the concentration given. The addition of liver extract accelerated the rate of ferrous sulfate absorption but hydrochloric acid had no influence (183).

Evidence was obtained suggesting that copper is not excreted following ingestion but that it is utilized by the digestive tract in a manner similar to iron (184). Barium, as barium chloride, is not absorbed from the stomach but is absorbed from the intestine. Food in the lumen hinders its absorption, while inorganic sulfates may precipitate it (185).

Large seasonal variations in calcium absorption were found in three out of six human subjects, the absorption being lowest during late winter and highest during summer. This fluctuation was not affected by vitamin-D administration. Magnesium absorption did not show this seasonal fluctuation (186). Substances in the outer

layer of wheat germ affected absorption of calcium in man and the addition of calcium salts to wartime wheatmeal bread was recommended (187). Calcium absorption was increased when administered with amino acids or peptone-glutamic acid mixtures (188).

Miscellanea.—Of extreme importance to experimental work on intestinal absorption was the determination of the surface areas of the intestinal mucosa in the rat and the cat. In both jejunum and ileum the mucosal area in relation to the serosal area was found to be higher in the cat than in the rat. In both species the ratio of the mucosal area of the entire small intestine to the body weight was constant and similar (189).

By employing radioactive sodium as a tracer, the sodium ion was found to move in both directions across the intestinal epithelium, the movement from intestine to blood occurring even against concentration gradients and while movement in the opposite direction was going on. In general there was a descending aboral gradient in sodium movements in both directions. The total turnover rate of sodium between intestine and blood was very high, being approximately equal to the total plasma sodium in eighty-three minutes (190). Histotoxic anoxia produced in dogs by intravenous administration of potassium cyanide did not influence absorption of chloride, sodium, sulfate, and water from intestinal loops of barbitalized dogs (191).

Most drugs, including epinephrine and morphine derivatives, are absorbed from the oral mucosa in insignificant amounts. However, strychnine and picrotocine are rapidly absorbed (192). Absorption can occur through the stratified epithelium of the first three compartments of the lamb's stomach. Orthoiodohippurate introduced into the rumen isolated between ligatures was detected an hour later in the urinary bladder (193). Penicillin is absorbed poorly from the digestive tract when given by mouth because it is destroyed by the acid but not by the pepsin of the stomach. Penicillin given orally is absorbed in patients with pernicious anemia because of the achlorhydria (194).

Quinine dihydrochloride was absorbed five to six times as rapidly as quinine sulfate from isolated intestinal loops of dogs (195). The difference between the rates of absorption of the two salts was not due to differences in water solubility since the free base was less soluble than the salts but was absorbed nearly as rapidly as the dihydrochloride (196).

Acetate is absorbed by the gut and trapped by the liver, resulting in an increase in blood volatile fatty acids (197).

Sulfathiazole is absorbed from the dog's rectum when introduced in suppositories (198) but absorption of sulfanilamide by rectum is less than by mouth (199). Potassium bromide and sodium salicylate are also absorbed to some extent by rectum. Magnesium sulfate may be absorbed from the rectum of children in toxic amounts (200).

Stimulation of the midbrain (substantia grisea on both sides of the third ventricle, very close to the Vicq d'Azur tract) with Hess's implanted electrodes in cats produced a great desire for food, accompanied by restlessness (201). In a self-study of appetite the effects of changes in the diet, prolonged fasting, and realimentation were studied (202).

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KIDNEY[1]

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The war has increased considerably investigation of the role played by the kidneys in shock. Search for antipressor drugs of value in hypertension continues actively along with further analysis of renal pressor, antipressor, and depressor components and their related systems. Critical reviews and discussions of the relationship between essential hypertension and experimental renal hypertension give evidence that the link between the clinical syndrome and the various experimental attempts designed to duplicate it has not yet been forged. Quantitative analysis of kidney function as affected by diet, vitamins, hormones, drugs, poisons, and other influences progresses.

Methods

Renal blood-flow measurement.—Convenient and accurate measurement of the diodrast clearance at low plasma concentrations of diodrast to estimate plasma flow through secretory renal tissue is achieved by improvement in the chemical determination of diodrast-iodine in blood (1). The value of the estimates rests on the constancy, under different conditions, of the extraction ratio of diodrast, determined from arterial and renal venous blood. The isolated perfused dog's kidney gives a lower ratio, 0.62 (2), than the 0.74 (3) and 0.87 (4) previously reported on the explanted kidney of the unanesthetized dog. The authors caution against applying their result for the isolated kidney to the intact animal, since the ratio falls steadily during an experiment and is also dependent on perfusion pressure. This is further evidence of the need for a careful critique of the conditions of kidney experiments before applying their results. An important lacuna in the use of diodrast and sodium para-amino hippurate clearances in man to measure effective renal plasma flow is filled by reports of direct measurement of renal venous blood samples from unanesthetized subjects

[1] This review should cover the period July 1, 1943 to June 30, 1944. Unfortunately, due to restrictions imposed by war conditions, most foreign journals have not been available to the reviewer.

obtained through a long rubber catheter threaded through an antecubital vein (5). In eight determinations, an average extraction ratio of 0.88 was found, which compares favorably with the results for diodrast and the dog's explanted kidney. This method will prove useful in extending knowledge of kidney function in man.

Plethysmographic methods for measuring blood flow in extremities have been extended to the kidney in animals (6): the renal vein is compressed for a few seconds by an electromagnetic clamp to make a reading of the rate of increase of the renal volume. Deviation of heparinized renal blood from the circulation for direct measurement, by cannulating the left ovarian vein and constricting the central portion of the renal vein, is also described (6).

Anatomy and Pathology

Glomerulus.—Fluorescent granules are sometimes present in the glomerular pole of the human kidney. They are absent in normal and hypertensive dogs. Their incidence is increased with age and they appear to be especially associated with scars. Their significance is doubtful (7).

Nephrosclerosis.—Lesions in the kidney similar to those seen in periarteritis nodosa, rheumatic fever, and malignant hypertension are reported by Selye & Pentz in unilaterally nephrectomized rats after desoxycorticosterone acetate overdosage (8). The authors state that these diseases are "usually preceded by infection, exposure to cold or other damaging agents . . . we believe that the above-mentioned diseases are, at least partly, caused by an abnormal (probably excessive) adaptive response of the adrenal cortex." They refer to unpublished results of Selye, who found a high sodium chloride diet in unilaterally nephrectomized rats, combined with exposure to cold and other strain-producing factors, produced the same results as the overdosage with the steroid (9). (See also the subsequent section on the effect of hormones.) Overdosage with desoxycorticosterone and a high salt diet in rats causes nephrosclerosis without preliminary unilateral nephrectomy (10, 11). Of other steroids, only progesterone acts somewhat similarly (12). A relationship between periarteritis nodosa and experimental perinephrosclerotic hypertension is described (13).

Acute renal failure or chronic renal lesions can be produced by proper control of dosage of low viscosity methyl cellulose, which appears to block and fill the glomeruli. Stabilization of a chronic

lesion without further dosage can occur. Subsequently, acute necrotizing vascular disease not confined to the kidneys may occur and lead to death. The pathological changes found are correlated with the usual urinary findings in progressive renal failure (14).

Diets deficient in the heat stable fraction of vitamin B, with thiamine added, cause hypertension in the rat. While at first the hypertension is reversible, it later becomes persistent. Diets markedly deficient in vitamin B_2 are less active in this regard than a moderate degree of deprivation. Other nutritional factors are probably involved secondarily, since a high protein diet causes renal lesions arrested by feeding increased vitamin B. The pathological changes found in the kidneys of these hypertensive rats are sclerosis of the interlobular arteries and afferent arterioles, "simplification of the glomerular pattern and thickening of the capillary basement membrane," and areas of ischemic atrophy of both cortical and medullary parenchyma (15).

The differential diagnosis of terminal Bright's disease from malignant hypertension with renal failure is aided by renal function tests. Low diodrast secretory capacity, especially if the filtration fraction is low, despite the presence of hypoproteinemia, characterizes Bright's disease (16).

Phosphatase.—The value of histochemical methods continues to be demonstrated. The alkaline phosphatase excreted in urine, both in solution and in the sediment, is increased after uranium nitrate nephrosis in rats and rabbits and the regenerated tubular epithelium is poor in alkaline phosphatase (17). Wilmer finds alkaline phosphatase disappears or is almost gone from the tubules of rat and rabbit kidneys two to five days after complete obstruction of the ureter, when oxygen uptake by the kidney slices also falls. Ordinary histological techniques reveal no changes (18). Partial obstruction of the ureter, temporary complete, or permanent partial occlusion of the renal artery, and ligation of the renal vein all reduced tubular phosphatase, but to a lesser extent. The aglomerular toadfish, in captivity, does not secrete glucose and lacks tubular phosphatase. Wilmer concludes that phosphatase probably plays a role in the resorption of sugar by dephosphorylation of hexosephosphates and that the amount present in mammalian renal proximal tubules is probably correlated with tubular activity (19).

Reduced atmospheric pressure.—Repeated exposure of rats for twenty-seven days to low air pressures causes increase in kidney

weight, possibly due to an observed increase in its red cell content, with slight parenchymatous damage. After recovery for one month, extensive parenchymatous damage, consisting of calcification and shrinkage of the stroma with apparent ischemia, is noted (20).

Effects of Normal Plasma Components

Water.—Men deprived of water for three or four days show, in some instances, diminution in glomerular filtration rate and effective plasma flow. Large doses of sodium or potassium chloride, or urea, cause a diuresis with fall in the urine/plasma osmotic ratio. On a standard diet, the output of water apparently depends on the salt intake (21).

Fuchs summarizes his views on kidney physiology, emphasizing the importance of arteriovenous anastomoses, the role of interstitial fluid, and the possibility of resorption of urine in the "fornix apparatus" of the calyces. For extraneous reasons, adequate citations have had to be omitted (22).

Oxygen.—The arteriovenous oxygen difference of renal blood in eight normal human subjects was found to average 2.3 volumes per cent, in accord with the only other direct measurement reported for man, made under spinal anesthesia (5).

Repeated daily exposure of rats during twenty-seven days to low atmospheric pressure causes polyuria, enhanced by exposure to cold and diminished by heat. The excretion of phenolsulfonphthalein is not thereby affected, while by contrast other forms of anoxia (from carbon monoxide or cyanide) cause oliguria with reduced excretion rate of the test drug. Posterior pituitary extract prevents the polyuria (23). Kindred ascribes the hyperemia of low air pressure exposure directly to the effect of anoxia on renal blood vessels and believes that diuresis is secondary, in part, to increased glomerular permeability and pressure (20). Since equilibrium is usually considered to be reached in glomerular capillaries between plasma and filtrate, increased permeability would be manifest as filtration of larger molecules, with proteinuria, not reported here. It is more likely that changes in glomerular blood pressure and permeability are not significant in explaining polyuria and that adrenocortical and pituitary hormones are involved.

Glucose.—The kidneys have been found to add glucose to blood flowing through them, a phenomenon which accounts for the level-

ing off of blood sugar, rather than its continued precipitate fall, in eviscerated rats with intact kidneys as compared to similar but nephrectomized rats (24).

The role of phosphatase in the proximal convoluted tubules and descending loop of Henle in the secretion of sugar is discussed in conjunction with correlation of tubular activity and phosphatase content (19).

Protein.—In chronic proteinuria, electrophoretic methods confirm the previous finding by chemical methods that " . . . the rate of progress of renal failure is closely associated with the duration and degree of concentration of [urinary] globulin." Gamma globulin excretion appears to be the most reliable covariant. The fact that no urinary fibrinogen is found in progressive nephrotic nephritis suggests that the hyaline materials deposited in the kidneys of these cases is not derived from fibrinogen (25).

Amino acids.—Different alpha amino acids appear to be resorbed in the kidney of the dog in a similar fashion (26, 27). While one group of investigators ascribes the similarity to rapid metamorphosis of amino acids (27), Pitts offers evidence that a single renal transfer mechanism is involved, since "both alanine and glycine reversibly block creatine reabsorption" (26, 28). Furthermore, stable reproducible quantitative differences in the measurements of the excretion processes involved for alpha amino acids are found. Pitts explains the rather considerable differences by employing the hypothesis advanced by Shannon & Fisher (29) that the resorbed material A, in the tubular lumen, combines with an intratubular substance B to form a complex AB. This complex decomposes, as a first order process, delivering A into the peritubular interstitial fluid. Thus:

$$A+B\rightleftarrows AB\rightarrow B+A$$

The reported experimental results fit this hypothesis, if differences are assumed to exist in the reaction velocities of the amino acids studied.

No sharp renal threshold for the amino acids is found (26, 27, 28) but maximal capacity of tubular transfer may well have been reached for several amino acids (26, 28). No damage to kidney function (28) or consistent rise in blood pressure of normal (30) and renal hypertensive dogs (31) follows high amino acid or protein intake.

While Goettsch *et al.* (27) find no relationship between glomerular filtration rate and plasma amino nitrogen level, Pitts reports that glycine (4 to 20 mg. plasma amino nitrogen per cent) "led to an increase in filtration rate and renal blood flow with some decline in filtration fraction" (30). Renal resistance falls sharply, which fact probably indicates dilatation of both afferent and efferent glomerular arterioles. When plasma amino nitrogen levels reach 50 to 60 mg. per cent, filtration rate and renal blood flow fall with a rise in filtration fraction, probably occasioned by constriction of both sets of glomerular arterioles.

Urea.—Variations in endogenous urea clearance in two normal men with changes in water excretion rate and urea concentration are detailed (32). Our knowledge of the excretion and resorption of urea, long of interest to clinicians as well as physiologists, is put on a much firmer basis by Dole (33). The trenchant value of logical and mathematical analysis of physiological phenomena, after explicit statement of the assumptions and limitations involved in the process, is only belatedly receiving recognition: American journals usually do not publish nonexperimental contributions, regardless of their merit. Dole succeeds in developing a working physical-chemical model of two-stage urea resorption which agrees well with the data on urea clearance gleaned from the literature. The permeability of the distal tubular wall to urea is found to be roughly a thousand times less than that reported for the ox erythrocytes.

Creatine.—Creatine competes for absorption by the same renal mechanism with glycine (28), alanine (26), and probably other alpha amino acids. Glycine has a higher affinity than creatine for this carrier (28).

Choline and phospholipid.—Young rats suffer greatest damage to their kidneys as a result of choline deficiency when kidney and liver phospholipid content and turnover are normally greatest. The choline deficiency reduces the phospholipid content, which change the authors consider to be the primary damaging agency (34).

Phosphate.—The rate of renal tubular resorption of phosphate appears to be proportional to glomerular filtration rate in man (35). The quantity of inorganic phosphate resorbed is essentially independent of plasma concentration at plasma levels between 10 and 50 mg. per cent; it is somewhat affected by plasma concentrations

between 3 and 10 mg. per cent, while complete resorption occurs with lower inorganic phosphate levels (36).

Effects of Abnormal Plasma Components

Protein.—The protein excreted in multiple myeloma is reported to be beta globulin (25, 37). Why it is excreted only in some cases of Bence-Jones proteinemia is still unknown. The progressive renal failure in this disease is found to be secondary to mechanical blocking of the nephrons as a result of a continued high concentration of globulinuria (37).

Galactose.—About 40 per cent of galactose filtered by the glomeruli of dogs is resorbed, irrespective of galactose plasma and filtrate concentration. Thyroxin does not affect the result. While these results are compatible with passive diffusion through tubular epithelium, the authors believe a transfer mechanism is involved (38).

Sucrose.—Large doses of sucrose cause severe hydropic degeneration in both normal and hydronephrotic rabbit kidneys. While goldfish, with glomerular kidneys, are similarly poisoned, the aglomerular kidneys of the toadfish, which contain no phosphatase and do not secrete sucrose, are unaffected (39). On this basis, Wilmer concludes that injury to tubules requires the presence of sucrose within the lumen of the tubules. Since in hydronephrosis the urine is not concentrated, a minimal filtrate (and so plasma) sucrose concentration is considered essential for poisoning. The failure of phlorizin in rabbits and rats to protect against sucrose damage, although sucrose resorption is thus prevented, argues against the necessity of active tubular absorption of sucrose for injury. Wilmer therefore concludes that diffusion of sucrose from the tubular lumen into the epithelium is adequate for poisoning. About 6 per cent of sucrose is estimated to diffuse back into tubules from glomerular filtrate in phlorizinized man and animals, and about 20 per cent is normally resorbed. (In man, there is some disagreement concerning this latter figure, as one observer found identity of inulin and sucrose clearances.) The dependence placed by Wilmer on the immunity of aglomerular toadfish to sucrose poisoning as a basis for rejecting diffusion from peritubular capillaries as a route of sucrose poisoning does not seem warranted. The lack of intratubular phosphatase in this fish may well be the deter-

mining factor. Furthermore, since diffusion would be accelerated in the distal tubules, where the urine is more concentrated, epithelial damage would be expected in this portion of the nephron on Wilmer's hypothesis. However, this is not the case.

Sulfonamides.—Acetylsulfanilamide appears to be synthesized elsewhere than in the kidney after sulfanilamide administration (40). It is filtered through the glomerulus at varying plasma concentrations and urine flows and is not subject to tubular secretion in rabbit and man (40, 41). Sulfanilamide clearance is also independent of urine flow and plasma concentration, but this drug is partially resorbed, averaging 30 per cent of inulin clearance in the rabbit (41) and 45 per cent in man (40).

Concern with the toxic manifestations of sulfonamide therapy has prompted further investigation of its mechanism, prophylaxis, and therapy. Hematuria in twenty rabbits given sulfathiazole develops less easily when the urine is alkaline. The sources of hematuria are in all instances, except possibly one, consequent on trauma (no doubt due to crystals of the drug) in the urinary tract exclusive of renal parenchyma (42).

The relation of pH to solubility of sulfadiazine in dog's urine is the same *in vivo* and *in vitro*, with a sharp rise in solubility when the pH exceeds 7. Sodium bicarbonate is recommended for alkalinizing the urine and, in mild solution, for retrograde lavage of the urinary tract after sulfonamide obstruction occurs (43).

Evaluation of various methods for promoting rapid elimination of sulfadiazine, because of toxic manifestations, indicates the greatest and most prolonged increase in drug excretion follows strong alkalinization of the urine by sodium bicarbonate administration. Where the need is for rapid decrease in urinary drug concentration, intravenous infusions of large volumes of 5 to 10 per cent glucose in water is most rapid and the only therapy which markedly increases drug excretion. Intravenous saline is definitely inferior. Forcing of water orally is similar to, but slower than, glucose infusions in reducing drug urine concentration (44).

If sulfonamide crystalluria is avoided, the drug itself may well have a beneficial influence in acute glomerulonephritis and other acute renal disease. However, toxic nephrosis apparently not due to obstruction by crystals, may be a rare complication and may become chronic (45, 46, 47).

Mercury.—As a test of the adequacy of actual filtration rate in

reaching the levels required in the modern theory of the place of glomerular filtration in renal function, anesthetized dogs, poisoned by mercuric chloride to prevent tubular resorption, were rapidly infused with about 700 cc. of 5.4 per cent glucose (48). A tremendous diuresis, with accompanying dilution of the blood and rise in arterial pressure, ensues. If renal blood flow is assumed normal, as in unanesthetized dogs, during this period, about 9 per cent of blood (13 per cent of plasma) passing through the kidneys is filtered. This finding is compatible with present theory.

Carbon tetrachloride.—Corcoran, Taylor & Page report in full a case of poisoning by carbon tetrachloride fumes, with complete recovery following treatment with 400,000 units of vitamin A daily (49). Edema, oliguria, proteinuria, decreased diodrast, and inulin clearances with decreased filtration fraction, and reduced capacity for diodrast excretion were found initially. While the blood pressure rose later, presumably secondary to the renal damage, cardiac output fell, probably as a result of marked peripheral vasoconstriction. The authors suggest that renal edema diminishes renal pulsation and activates to a higher level the renin pressor system; although the renal pressor amine system may here be operative, in view of the patient's abnormally increased blood pressure response to epinephrine. The pronounced fall in glomerular filtration rate and filtration fraction are tentatively believed by the authors to result both from reduced effective intraglomerular filtration pressure caused by renal edema and from diseased patent, but nonfiltering, glomerular capillaries. We consider that afferent arteriolar constriction is at least as likely to coexist, in view of the greatly increased peripheral resistance. "Vicarious clearance"[2]—inclusion in the excreted urine of diodrast secreted by active tubules, but derived by diffusion from blood supplied to impotent tubules—is suggested by Corcoran *et al.* to explain the apparent hyperemia found in this case of poisoning. Renal plasma flow is given in terms of flow per unit of functioning tissue capable of excreting 1 mg. diodrast as iodine. It seems probable to us that maximal capacity for diodrast excretion is reduced in the still functioning but poisoned tubules, along with complete loss of that capacity in others, and that dependence on "vicarious clearance" to explain the apparent increase in blood flow per unit excreting

[2] "Vicarious clearance" is derived from "vicarious hyperemia," a somewhat different concept advanced by Smith (50).

tissue is unnecessary. In fact, "vicarious clearance" may rarely be of quantitative importance, since the direction of interstitial fluid flow for active proximal convoluted tubules is mainly away from epithelium towards peritubular capillaries, because of the large volume of filtrate resorbed by that route (51).

Chloroform.—As has been shown for uranium nitrate poisoning, the decompensating kidneys of senile dogs with reduced alkali reserve and ability to excrete phenolsulfonphthalein are found to be more resistant to chloroform poisoning than are normal controls (52). The increased resistance of the senile kidneys is correlated with the occurrence in the proximal convoluted tubules of a less differentiated, flattened epithelium, which is apparently less efficient but more resistant than normal cells. Similar results are referred to for the liver, after a repair process.

Effects of Vitamins

Vitamin A.—Interest in the renal effects of vitamin A has been prompted by a favorable report concerning its therapeutic use in hypertension (53). In unanesthetized dogs, 5,000 to 50,000 units of vitamin A in corn oil daily are without effect on glomerular filtration rate, effective renal plasma flow, and maximal tubular secretory capacity for diodrast or *p*-aminohippuric acid. Larger doses (200,000 units daily) cause increase in these measurements, particularly maximal tubular capacity, without change in filtration fraction. This change is regarded as similar to that produced by a fish diet in harbor seals and high protein in normal and hypertensive dogs (54). It is worthy of note that the changes reported do not indicate hyperemia measured in terms of flow per unit maximal secretory capacity (Tm). The possibility that the corn oil (which contained no fatty acid radicals), rather than the vitamin, is responsible for the experimental findings is not excluded—a possibility of importance in the light of other reports (55, 56).

In normal and hypertensive patients, vitamin A (the menstruum is not stated) in daily doses between 100,000 and 400,000 units for five to ninety days causes no fall in blood pressure (57). In some cases, the same changes in renal dynamics and secretory capacity are found as described above for high vitamin-A dosage in dogs, along with increased cardiac output, probably secondary to tachycardia. It is the impression of the investigators that some substance other than vitamin A, present as an impurity, may be the

active principle. In the later report, Page and his associates find increased renal function in chronic nephritis on high vitamin-A dosage, when bile salts are added to promote its intestinal absorption (58).

Ascorbic acid.—The study of tissue cultures of chick renal proximal tubule epithelium is continued by Chambers and his coworkers. They find no stimulation of the secretory activity of the closed sacs formed by clumps of these cells by *l*-ascorbic acid, although activation of cell proliferation and growth occurs (59). Direct appplication of results derived from avian tissue to mammals must be cautious since differences can be striking, for example the great sensitivity of chickens to sodium chloride (60).

Effect of Hormones

Epinephrine.—Small doses of epinephrine in frogs reduce diodrast clearance (effective renal plasma flow) but not creatinine clearance (glomerular filtration rate) so that filtration fraction rises. Massive doses reduce all the measured quantities, including filtration fraction and the number of functioning glomeruli (61). The author thereupon concludes that efferent arteriolar constriction occurs in frogs with small doses of epinephrine, while afferent constriction is caused by large doses. He writes: "In the normal frog, unlike mammals, afferent control of the glomerular circulation plays an important role in the regulation of glomerular activity." It is a widespread misconception that the afferent arterioles are not important renal regulators in mammals: the opposite is the case (51, 62, 63, 64). Conclusions concerning the primacy of either set of glomerular arterioles in a given situation cannot be sound without knowledge of the blood pressure. In man, as in the frog, small doses of epinephrine decrease the effective plasma flow but leave unchanged the rate of glomerular filtration (65, 66). Yet these results are best explained by concomitant changes in both afferent and efferent arterioles (62).

Ephedrine and paredrinol have renal effects[3] in man similar to those of epinephrine (66). Again we must disagree with the conclusion that this implies constriction of efferent arterioles (66).

Parathyroid hormone.—The role of the kidneys in the influence

[3] The extrarenal circulatory effects of epinephrine, ephedrine, and paredrinol are reported fairly completely and elucidate the systemic actions of these substances (66).

of parathyroid hormone on calcium and phosphorus metabolism has been further clarified. Both nephrectomy alone and parathyroid hormone with or without nephrectomy produce bone lesions (67) and serum calcium elevation (68) in the rat. Hence this hormone does not depend for its activity on an increased urinary excretion of phosphate (67). The pathological changes in bone caused by parathyroid hormone are both qualitatively and quantitatively different (irrespective of whether or not the kidneys are present) from those produced by nephrectomy alone (67).

Thyroid.—In patients with abnormal thyroid activity under standardized conditions, the urea clearance is subnormal with reduced basal metabolism; with increased basal metabolism, the results scatter widely, with a suggestion of increased clearance (69). In dogs, thyroid increases glomerular filtration rate (70, 71, 72) and the tubular capacity for diodrast secretion (Tm_D) (71 ,72), as does thyroxin (71). Thyroid also increases effective renal plasma flow and Tm_D in the dog both before and after simple and total hypophysectomy (72). The tubular capacity to resorb glucose after thyroid or thyroxin (71), as well as galactose after thyroxin (38), is also enhanced. It is not as yet clear whether any or all of the renal effects of thyroid administration are directly renal, secondary to other hormonal interactions of the thyroid, or a result of increased systemic metabolism.

Thyroxin doubles water intake and urinary output in rats and confers marked resistance to water intoxication with striking diuresis of low chloride content urine. This protective action is largely abolished by adrenalectomy (73).

Androgens.—Various androgens increase the weight of the kidneys in female mice (74). Increasing the intake of potassium chloride and so loading renal excretion of this salt does not affect the increase of kidney weight found in castrated male mice given methyl testosterone (75).

Selye & Rowley find that methyl testosterone prevents completely the development of experimental nephrosclerosis otherwise seen in rats (especially unilaterally nephrectomized ones) after sodium chloride and desoxycorticosterone administration. They make the interesting suggestion that the renotropic and masculinizing effects may be separable, thus providing a drug which may have therapeutic value, especially in the toxemias of pregnancy (76).

Methyl testosterone caused nitrogen retention, persistent gain in weight, and marked increase in creatinuria in four cases of Simmonds' disease, and in addition was of clinically apparent therapeutic benefit (77).

Hormones and other factors in water excretion.—Water excretion by the kidney is especially influenced by adrenocortical hormone and desoxycorticosterone, by the secretions of the thyroid and pituitary glands, by the inorganic salts and other blood solutes, and, of course, by the concentration of water itself. Many of these influences are not directly renal, being effective through other routes which are being actively explored. The various factors concerned in water excretion are reviewed under their respective headings, except that water excretion in hypertension is treated in the section on experimental renal hypertension and nephrosclerosis.

Adrenocortical hormones.—The complementary relationship between desoxycorticosterone and a high sodium chloride diet in the production of nephrosclerosis has already been mentioned (8, 11). Potassium does not appear to take part in this phenomenon in either the chicken, in which the test is most sensitive (12), or in the mouse (75). Rats under a regimen of desoxycorticosterone acetate (DCA) react by increasing their sodium chloride and water intake, though polydipsia may here be secondary to the increased salt appetite (78). The likelihood that DCA acts directly on kidney tubules is strong, since Kendall's whole cortical extract and compound E (but not A) stimulate secretion within chick proximal tubule epithelium sacs in tissue culture (59).

Both the adrenocortical hormone and DCA (79), as well as repeated exposure to water intoxication (80), protect normal rats from water intoxication, increasing diuresis without change in the excretion rate of chloride (79). Thyroid protection, as has been noted, is almost abolished by adrenalectomy (73). Adrenalectomized rats, while responding like normal ones to water intoxication, if given replacement therapy one day postoperatively, respond later fairly erratically for no known reason (81, 82). Gaunt reviews the relationship of water intoxication to the adrenal cortex (82) and other endocrine factors (83). It appears that a direct renal effect by the adrenal cortex is likely, perhaps one not as yet reproduced by current replacement therapy.

The polyuria produced in normal dogs by DCA superficially resembles mild diabetes insipidus, but pitressin, even in doses many

times greater than that required to control a corresponding degree of true diabetes insipidus, is only partially effective (84). DCA administration accentuates the severity of diabetes insipidus in dogs, but not cats which are also unresponsive to adrenocortical hormone. In diabetes insipidus dogs, as well as in normal ones, DCA first reduces tubular resorption of water. Only after doses larger than 10 mg. daily does glomerular filtration rate also rise. Cats exhibit no such changes (84). These results for the effect of DCA on glomerular filtration rate are similar to those in dogs for adrenocortical extract,[4] which causes, however, either little change or a slight fall in renal blood flow and tubular diodrast capacity (72). The amount of protein and salt intake seems to play a role, but less than in diabetes insipidus, since polyuria fluctuates with these dietary components. Winter & Ingraham conclude that participation of the adrenal cortex in the establishment of diabetes insipidus is still unproven (84).

Pituitary hormones.—In normal dogs and those after simple or total hypophysectomy, anterior lobe hypophyseal extract (and thyroid) increases glomerular filtration rate, effective plasma flow, and especially tubular capacity for diodrast. Adrenocortical extract in hypophysectomy (simple and total) tends to reduce slightly diodrast clearance and tubular capacity. Because of the rapidity with which anterior pituitary extract restores the marked drop in inulin and diodrast clearances and especially tubular diodrast capacity occasioned by hypophysectomy, as well as the considerable difference between its effect and that of adrenocortical hormone, Heinbecker and his colleagues conclude that the renal action of the anterior pituitary hormones is essentially direct (72).

In canine diabetes insipidus, the increased rate of glomerular filtration caused by thyroid completely accounts for its diurectic action and its reduction in the effectiveness of pituitrin therapy. Where the polyuria is latent, however, the diuretic action of thyroid is very considerable and reduction in tubular resorption of water must be invoked along with increased filtration to explain the phenomenon (70). There is a deficiency in the ability to concentrate not only sodium chloride, in diabetes insipidus, but also nitrogen. No evidence is found of abnormal nitrogen metabolism, nor a dependence on the caloric content of the diet. Polyuria paral-

[4] In the *summary* to this paper there is stated a different conclusion from that in Table 1 and the section on *results* (72).

lels nitrogen intake but follows salt intake only on a high salt diet (85).

Hare, Hare & Phillips have carefully studied the relation between sodium chloride and water excretion in normal dogs and dogs with diabetes insipidus (86). They find no maximal rate of tubular resorption (no threshold) for chloride. Pitressin does not inhibit or otherwise affect its tubular resorption, although possibly some other pituitary fraction does. They find that water resorption is related to chloride resorption through the dependence of water resorption on the amount of pituitary antidiurectic hormone released, in turn, by stimulation of the hypothalamicohypophyseal mechanism by increase in the concentration of blood chloride. Hypertonic saline stimulates; hypotonic saline, glucose, and water all inhibit the secretion of this hormone. The concentration of chloride resorbed is dependent on the antidiuretic hormone because the latter determines the relative volume of water resorbed in which the chloride is dissolved. These considerations are consistent with a fixed ratio, in the normal dog, between concentration of chloride resorbed and concentration of plasma chloride, which is affected only moderately but quite consistently by variations in hormone concentration. The proposed system of antidiurectic hormone production sensitive to blood chloride concentration is promising.

Newborn infants excrete a markedly hypotonic urine and respond poorly to intramuscular posterior pituitary extract capable of marked antidiuretic effect in man. Their kidneys are relatively insensitive to this hormone (88).

Humoral Vascular Mechanisms Related to the Kidneys

At the present time, the basic observation that interference with renal blood supply consistently can produce experimental hypertension has stimulated search for the causal renal mechanism with a view to relating experimental and human essential hypertension. On the one hand, there is the renin system; on the other, the system of renal pressor amines: both continue to be actively analyzed. In addition, with a view to therapy, depressor and antipressor substances are engaging considerable attention. The renal hormones affecting blood pressure have been reviewed in condensed fashion (87).

Renin and related substances.—The terminology of the renin

system still differs among investigators. Page and his co-workers suggest that the substrate of the enzyme renin, previously called by them "renin-activator" and by the Argentine scientists "hypertensinogen," be changed to "renin-substrate (α_2-globulin)" or, more simply, "renin-substrate" (89). They consider that the enzymic character of renin has been well demonstrated (90), but that its relationship to essential hypertension, suggested by "hypertensinogen," is still unproven. Because of the confused terminology inevitable when contributions to knowledge from many laboratories are being made simultaneously, we indicate the current synonymous terms (89, 91):

$$\left\{\begin{array}{l}\text{renin-substrate}\\ \text{renin-activator}\\ \text{hypertensinogen}\\ \text{pre-angiotonin}\\ \text{pre-hypertensin}\end{array}\right\} \underset{\text{renin}}{\xrightarrow{\text{Enzyme}}} \left\{\begin{array}{l}\text{angiotonin}\\ \text{hypertensin}\end{array}\right\} \xrightarrow{\text{Enzymes}} \left\{\begin{array}{l}\text{angiotonase}\\ \text{hypertensinase}\end{array}\right\} \text{Inactive substance}$$

Preparation from hog kidneys of renin with a higher pressor activity per milligram of nitrogen than has previously been reported is described in detail. Electrophoresis suggests a homogeneous protein has been isolated (91). Criticism of this and similar methods of renin assay which depend directly upon the pressor response obtained is advanced by Plentl & Page (90) in a noteworthy analysis of the kinetics of the renin system. Quite correctly, they recommend assay of renin for its enzymic not its pressor activity. Test of the latter is confusing, since many of the renins made by different methods show large quantities of angiotonase, which destroys the pressor substance angiotonin formed by renin. Similar arguments apply to the assay of angiotonase. While assay of renin on the basis of its equivalent in angiotonin (hypertensin) has been reported (92), the method of Plentl & Page, for reasons they advance, seems preferable: it depends on no standard angiotonin or particular animal preparation, since it is simply the biological measurement of the reaction constant of the enzyme renin in a first order reaction.

While the premises, argument, and final conclusions reached by Plentl & Page seem to us quite sound, we find a few confusing errors in the mathematical expression given the argument. On page 371 of their article, equation (*6*) should read:

$$\log_e (\text{maximum activity} - \text{activity at } t)/\text{maximum activity} = -kt$$

Equation (*7*) should equate to $4.6\ -kt$, not kt.

Methods for assaying angiotonase are also given by Plentl & Page, with good demonstration of their reasonableness. Simple nomograms or formulas are derived for both renin and angiotonase determination. Experimental verification of the theory is seen especially in the good fit between their observations for a preparation of renin containing angiotonase and their theoretically derived curve.

Antirenin is produced in rabbits, guinea pigs, and in normal and hypertensive dogs by heterologously derived renins; homologous renins in dogs and rabbits are ineffective (93). Antirenin is not species specific in its ability to neutralize renin *in vitro*, except for antirenin from rabbits induced by human renin. It does not lower the blood pressure of hypertensive dogs. Antirenin is a pseudoglobulin. No antirenin is produced by hog liver extract or human kidney not containing renin (93).

The importance of the nervous system in the pressor action of angiotonin continues to be delineated. Page shows that rapid elimination of the central nervous system in cats and dogs by surgery or local anesthesia does not interfere with pressor response to angiotonin, while ordinary injury causes the usual fall in blood pressure with refractoriness to angiotonin (94). The kidneys and suprarenals are not involved in this phenomenon; rest restores angiotonin activity; only glycine and methyl isothiorea, of many substances studied, restore activity and they behave irregularly. The refractoriness is specific for angiotonin, since the pressor responses to epinephrine, tyramine, and methyl isothiourea are undiminished. Reduction in blood pressure does not seem to be the primary mechanism here: although angiotonin refractoriness is roughly parallel to the degree of blood pressure fall, restoring the blood pressure by infusions, once refractoriness has occurred, does not restore the pressor response. Severe hemorrhage likewise abolishes the angiotonin response. Page has found in blood a nonrenal vasoconstricting substance in shock after hemorrhage (95). While it is not clear whether this vasoconstrictor blocks the angiotonin effect, it may do so, even though Page notes no interference in the perfused rabbit's ear between this vasoconstrictor and that present in hypertensive dog or human blood.

Angiotonin is studied by means of crystalline pancreatic enzymes and is found to contain "at least three peptide linkages, one free terminal amino group, two aromatic, one acid, and one basic amino acid residue" (96).

Ogden expresses his view, not dissimilar to that held by others, that the renin pressor system is a normally operative homeostatic one which functions to maintain adequate pulse pressure and which is deranged both in experimental renal and essential hypertension (97).

The depressor substances found in the kidney are complex molecules of prolonged activity, not specific in their pharmacological actions on blood pressure and the heart in anesthetized and unanesthetized dogs (87). They are inactivated by oxidation. Renin, on the contrary, after destructive oxidation, forms depressor compounds. The depressor substances in the kidney appear to be independent of the renin chemical system.

Two pressor bases, only one of which has previously been reported, are found in the steam distillate of normal urine rendered alkaline with sodium hydroxide (98).

A difficulty with the attempt to implicate a shift towards an anerobic type of renal metabolism with formation of pressor amines as a factor in experimental or essential hypertension has been the lack of conclusive evidence of renal ischemia or hypoxia in this condition. Raske finds reduced respiration of slices of kidney from dogs with experimental renal hypertension, as well as reduction in their oxidizing ability measured by oxygen uptake and ammonia formation in the presence of added amines and amino acids (99). These slices also contain less amine and amino acid oxidase than normal. The results are related to the degree of renal artery constriction.

Antipressor action of parenteral ortho-quinoid epinephrine derivates (adrenochrome) is reported in rats by Oster & Sobotka (100). The adrenochrome appears to reduce the blood pressure only in rats with experimental renal hypertension. No toxic or febrile response occurs and a parasympathomimetic, directly muscular, or sympatholytic mechanism does not appear to be involved. The authors suggest that these epinephrine oxidation products act by destroying pressor amines or whatever substances are pressor in experimental hypertension.

Experimental Renal Hypertension and Nephrosclerosis

Barred Rock chicks are extremely sensitive to saline solutions. Provision of 0.9 per cent sodium chloride in place of tap water precipitates water intoxication and renal nephrosclerosis, probably the same as "blue comb" or "pullet disease," the avian analogue of

Bright's disease, the cause of which, it is suggested, is accidental salt poisoning (60).

In rats, a similar disease is produced by a high sodium chloride intake, by slightly less salt supplemented with desoxycorticosterone acetate or, less effectively, progesterone (10), and by the same methods still more easily, after preliminary unilateral nephrectomy (12). Large doses of the steroid and salt produce hypertension and pathological changes in kidney, pancreas, and adrenal capsule considered by the authors to be similar to those seen in human hypertensive heart disease (11). The protection afforded against this type of nephrosclerosis by methyl testosterone has been mentioned (76).

The production of nutritional hypertension by a diet deficient in the heat-stable fraction of the vitamin-B group has also been discussed (15).

The finding of antipressor adrenochromes (see above), active only in the experimentally hypertensive animal, suggests that the active principle is destroyed or inhibited by the adrenochrome (100).

Posterior hypophysectomy does not interfere with the development of renal hypertension in rats, nor does ablation after hypertension has occurred influence blood pressure, unless the anterior pituitary is also affected (101). If that portion is excised, blood pressure falls, but reaches normal only if hypertension is of less than one month duration (102). Purified adrenocorticotropic pituitary hormone restores the hypertension, while lactogenic hormone, serving as control, is without effect. Adrenalectomy or administration of adrenocortical hormone was not tested, probably because the importance of the adrenal cortex in renal hypertension is considered established.

In rats made hypertensive by partial ligation of renal arteries or perinephric scar, polyuria and polydipsia 75 per cent greater than normal occurs (103). If the procedure is unilateral, excision of the normal kidney increases the blood pressure and water intake; excision of the abnormal one has an opposite effect. It is suggested, without proof, that the polyuria is due directly to renal ischemia and hypoxia rather than to the intra- and extrarenal consequences of hypertension.

A high protein or urea diet fails to increase the blood pressure of renal hypertensive dogs (31).

A hypertensive dog reacts to shock like normal ones except that

no "peripheral vasoconstrictive substance" is found in its blood (104).

Sodium pentobarbital anesthesia and yohimbine, a sympatholytic agent, are each reported to lower the blood pressure of rats hypertensive for longer than seven to eight months, but are ineffective in rats hypertensive for much shorter periods. In normal rats, the anesthesia does not change blood pressure, while yohimbine may cause a slight increase (105). The authors of this report then suggest "that the renal pressor mechanism which initiates experimental renal hypertension is later superseded by a neurogenic mechanism mediated through the sympathetic nervous system."

While not strictly "renal physiology," the existence and characteristics of experimental neurogenic hypertension are related. Division of the depressor or buffer nerves is reported to cause hypertension in dogs, even during sleep (106). However, intracisternal kaolin is reported by Lambert & Wakerlin not to cause hypertension in their experience, nor in that of Page or Foà *et al.* (107).

Etiology and Pathology of Essential Hypertension

Inevitably, understanding of the etiology of human hypertension is implicitly sought in many of the current investigations of kidney physiology, especially those reviewed in the last two sections and in the succeeding one on the treatment of hypertension. If a particular treatment is effective in experimental renal or in human hypertension, it casts light on the underlying mechanism of the condition treated. If a therapy is proven effective, both in experimental hypertensive animals and in the human disease, it is presumptive evidence of their similarity; while failure in one points against an identical mechanism, although species differences may still be invoked.

A prime difficulty in equating experimental renal hypertension to human essential hypertension has been the failure to demonstrate the likelihood of the effective experimental agency arising clinically in man. Dietary deficiency in heat-stable fractions of vitamin B, high salt diets especially with doses of desoxycorticosterone acetate (8, 10, 11), partial constriction of the renal arteries, perinephric scar formation, roentgen irradiation of the kidneys, among the many reported methods, produce experimental hyper-

tension, but their counterparts have not been demonstrated in man, except as rare curiosities. Strain of the adrenocortical system has been suggested by Selye *et al.* to bridge this gap for the high salt-steroid type of nephrosclerosis (9).

If essential hypertension is often the result of local parenchymal renal disease, unilateral nephrectomy should frequently prove an effective therapy. Apparently, in only a very few cases has it restored blood pressure to normal.

Obstructive lesions of the main renal artery, corresponding to the Goldblatt clamp, are quite rare. They can produce hypertension and probably are somewhat more common than has been reported (108).

Therapies based on one hypothesis may prove efficacious for quite different reasons. The excellent results reported by Kempner for a rice diet (vegetable proteins substituted for those of animal origin) may be in this category (109). If they are substantiated, these findings would have important bearing on the etiology of essential hypertension, irrespective of the category in which they belong. It must be stated that in experimental renal hypertension, the quantity of animal protein in the diet is not material (31).

If either the renin system, hyperactivated by reduced renal pulse pressure or some other renal derangement, or the renal pressor amine system, activated by hypoxia, is suggested for the pathogenesis of essential hypertension, attempts to find special cases to test the hypothesis are indicated. In constrictive pericarditis, cardiac output, and particularly renal blood flow, are subnormal; glomerular filtration rate may be reduced; systemic venous pressure and renal filtration fraction are elevated (110, 111) In terms of blood flow per unit diodrast secreting capacity (Tm_D), these patients show greater ischemia than is usual in essential hypertension (111). The findings would have greater interest if the cases had also shown diminished pulse pressure, but two of the three cases reported had both normal blood and pulse pressures. As the authors point out, the elevated filtration fraction may be secondary to reduction in plasma proteins, which apparently was also found. We have noted the importance of this factor in renal hemodynamics (112). Operation to free the heart reversed all the observed abnormalities, but improvement in renal function occurred early, before venous pressure had yet fallen to normal (111). The case of carbon tetrachloride poisoning, with transient

hypertension presumed to be due to renal edema and reduced renal pulsation, has been outlined above (49).

If a homeostatic mechanism is involved in the maintenance of essential hypertension, it can be argued—it has in the past occasioned studies which belied this argument—that reducing blood pressure may be deleterious to hypertensives, unless the primary cause initiating the disturbance is itself removed. With this purpose in mind, an attempt to study the effects of spinal anesthesia on renal function has been made by somewhat outmoded methods (113).

An important investigation because of its direct approach is that of Dexter & Haynes. They have measured the amount of renin in the blood of various types of patients with increased blood pressure (114). They find renin only when the blood pressure is rising acutely (one case of eclampsia; two of severe preeclampsia, and one of fulminating acute glomerulonephritis were studied). None is found in the mild toxemias of pregnancy, moderate acute glomerulonephritis, and chronic essential hypertension of all degrees of severity. These results are in accord with those of Dell'Oro & Braun-Menendez (115). They suggest that the renin pressor system may be involved only initially in the development of hypertension.

Page finds that rabbits' ears, refractory to vasoconstriction or perfusion with canine hypertensive serum, also fail to respond to human hypertensive serum, while continuing to react to other constrictors. This suggests a similarity in their pressor substances (95).

Schneider has proposed a general theory of disease, "the growth concept of nervous integration," which he seeks to apply to renal hypertension (116, 117). It is unrigorous, pseudomathematical, and quite hypothetical. In essence, an imbalance between the endocrine and nervous controls of blood pressure is suggested.

There have been various reviews concerning the etiology of hypertension (87, 97, 105, 118 to 121). Page and his collaborators suggest the use of spinal or pentothal anesthesia to separate neurogenic from "renal" hypertension (119, 122). Page presents an excellent analysis of the problem of the pathogenesis of hypertension, stressing particularly the lack of evidence for the necessity of ischemia or anoxia in the kidney to produce renal hypertension (120). Smith and his co-workers also review the problem compre-

hensively. They conclude that "the kidney appears to be the victim rather than the culprit" (121).

Treatment of Hypertension

Experimental hypertension.—Suspension of the kidney, after prior constriction of the renal artery, is reported to lower the blood pressure of hypertensive dogs (123). The kidney is moved 5 cm. so as to facilitate, supposedly, emptying of the renal vein. Possibly the arterial constriction is also reduced by the procedure. Apparently, in man, following operation for constrictive pericarditis, increase of renal blood flow to normal occurs while venous pressure is still significantly elevated (111). This is not in accord with the hypothesis advanced as a basis for renopexis.

Vitamin A did not lower the blood pressure of hypertensive dogs, except for one lot of the concentrate (56, 124). It is likely that the suspending oil is involved. Grollman reports that oxidized marine oils contain an orally effective principle unrelated to viamin-A content, probably an oxidation product of fatty acid, which reduces the blood pressure of renal hypertensive rats and dogs. He was able to concentrate the responsible substance three-fold (55).

In pilot experiments, no changes in the blood pressure of experimental hypertensive dogs are caused by administration of the vitamin-B complex, ascorbic acid, or vitamin E (124).

Wakerlin and his collaborators find that the antipressor effect in renal hypertensive animals of impure renin depends on the presence of some other renal substance, not present in hog liver. The active principle is partially heat-stable and is not antirenin in the immunological sense (125, 126).

The use of *o*-quinoid epinephrine derivatives has already been discussed (100).

The therapeutic promise of these various antipressor substances is still to be fulfilled in human hypertension.

Human hypertension.—The existence of intrinsic or extrinsic obstruction of the main renal artery, simulating a Goldblatt clamp and causing the human analogue of experimental renal hypertension, has been demonstrated. The treatment of this condition is, of course, surgical but diagnosis of this rare condition is difficult. Apparently more cases exist than are reported (108). Smith *et al.* review the group (121).

Unilateral nephrectomy as a treatment for hypertension will succeed only if a local renal lesion is its cause and the vasoconstriction is systemically reversible. Sensenbach reviews seventy-five cases of hypertension treated by unilateral nephrectomy (127). Of seventy-five cases, five were followed for more than two years and maintained a normal blood pressure; about one-third had normal blood pressure but were followed for less than this period; and one-third exhibited a fall in blood pressure, but not to normal. Chronic pyelonephritis was the commonest pathological finding. Sensenbach concludes that removal of a kidney with any function is likely to increase the hypertension, even when the other seems quite normal. Two cases of unilateral nephrectomy for pyelonephritis with normal blood pressure for more than two years after operation are reported (128, 129, 130). Smith and his collaborators record negative results for unilateral nephrectomy in sixty-nine out of seventy-six cases reviewed (121). However, this figure seems unduly high since the twenty positive cases inadequately followed or controlled should be excluded altogether, if rigid criteria are to be imposed, rather than reclassed as failures. Furthermore, no similar winnowing of the negative results seems to have been pursued, since their number was left intact. While it would seem that unilateral nephrectomy is somewhat more effective a treatment than is stated, we agree with the authors' conclusion: "Unilateral renal disease is rarely a cause of hypertension in man."

Kempner reports that a very restricted monotonous diet emphasing rice and excluding most animal protein was never harmful in 150 cases of renal and hypertensive vascular disease and was beneficial in 73 per cent of them (109, 131). Cardiac manifestations are diminished and blood pressure and blood nonprotein nitrogen fall towards normal. Apparently bed-rest is a part of the early treatment and the cases seem advanced, since renal and cardiac decompensation are stressed.

The promising results obtained with vitamin A therapy have been discussed in the section on vitamin A.

Toxemia of pregnancy.—Veratrum viride, an alkaloid, given orally to ten pregnant women (five pre-eclamptics, four hypertensives, one normal) caused a considerable fall in systolic and diastolic blood pressure, most marked after about two hours. Urine output and urea clearance were concomitantly depressed (132).

Miscellaneous

Pain.—The mild pain produced by contact with cold water causes inconclusive changes in human renal function. Pressure applied to the head, however, so as to cause severe headache, reduces effective renal plasma flow and glomerular filtration rate, and increases filtration fraction and blood pressure. Urine output falls (133).

Anesthesia.—The effects of intraperitoneal administration of 30 mg. per kg. sodium pentobarbital on blood pressure and renal function are reported (134). The blood pressure is significantly elevated, an average of 18 mm. Hg. but the glomerular filtration rate, effective renal plasma flow, and tubular diodrast capacity were abnormal in only three of thirty-seven experiments. Some oliguria is found about half the time. When renal failure occurs, there is marked oliguria with concurrent fall in renal blood flow and filtration rate, independently of whether blood pressure is elevated or depressed. It is therefore suggested that severe oliguria may be a more sensitive indication of pentobarbital toxicity than fall in blood pressure. The authors believe that renal failure may be a result of renal vasoconstriction, and that the usual maintenance of renal flow and filtration in the face of centrally evoked increased blood pressure is probably a consequence of an autonomous response of the kidney to the increased blood pressure by constriction of afferent arterioles, rather than a direct response to the drug. This last suggestion is based on the supposition that efferent constriction characterizes peripherally active drugs such as epinephrine, renin, and angiotonin. While this statement seems to us incorrect for reasons already adduced (51, 62, 63), the conclusion that afferent arteriolar constriction usually occurs under pentobarbital anesthesia is sound. It appears likely, however, that a drug which can cause toxic renal effects irrespective of blood pressure probably has a direct renal effect in the nontoxic cases as well. This effect would be in addition to an autonomous response by the kidneys to increased blood pressure, as well as, perhaps, to the central sympathetic stimulation suggested by the authors to explain the elevation of blood pressure.

Hydronephrosis.—Hydronephrosis induced in rabbits develops in the kidney an intrapelvic pressure of 7.5 mm. Hg in three days. After six to sixteen days, the pressure reaches 22.5 to 27.5 mm. Hg and falls to about 16 mm. Hg in sixty-seven days (135). These

pressures are not sufficient to prevent glomerular filtration so that urine formation continues at a slow pace. Whether pyelovenous reflux occurs is not known, nor is there an adequate explanation for the failure of more than a small quantity of urine to appear at the renal pelvis when pressure is relieved. Histologically, the glomeruli are considered fairly normal while the tubules are "disturbed." Two to five days after ureteral obstruction, little or no "alkaline" phosphatase is found in the tubules, although otherwise the epithelium appears normal (18). On the sixth day, oxygen uptake of kidney slices is definitely reduced (19).

Shock and related conditions.—The renal failure sometimes seen after crushing injuries to the extremities has been ascribed to lack of adequate renal blood flow, to obstruction of the lumen of the nephrosis by casts, and to a primary toxic effect on renal parenchyma. It is not yet clear whether the response of the kidney in "crush" injury is merely an exaggeration of its response in shock *per se*, although most observers do not believe so (104). Scarff & Keele refer to previous findings that renal blood flow, despite adequate blood pressure, may fall to perhaps 10 per cent of normal and that kidney volume in dogs falls when hemoglobin is injected intravenously (136). They find in rabbits extensive damage to the postglomerular secreting tubules, rise in blood urea for three to four days, followed by recovery or death, after renal arterial occlusion of one to two hours duration. The lesions they consider to be quite similar to those in the "crush" syndrome and to offer support for the view that inadequate renal blood flow is the prime cause of the kidney failure.

Bing finds, in unanesthetized dogs, no effects on renal plasma flow, filtration rate, and tubular capacity for glucose resorption after intravenous infusions of myoglobin or hemoglobin. Methemoglobin, in dogs rendered acidotic but not in normal ones, causes a fall in the measurements of renal function (137, 138, 139). "Hydropic degeneration of the proximal convoluted tubules, cellular necroses in the distal segment and plugging of the collecting tubules with hyaline and in some instances with pigmented casts" characterize the renal lesion. Glomerular damage and dilatation of tubules are absent. Acidosis itself is without effect, unless the drug used also causes methemoglobinemia (as with lactic and hydrochloric acids). The anuria followed by death seen in blackwater fever is associated with methemoglobinuria and alkalinization has

been of value in this disease. Bing suggests that his experimental findings are similar. In mismatched transfusions and "crush" syndrome, methemoglobinemia does not appear to be present. Bing believes it likely that in these conditions in man either the same mechanism prevails, unrevealed by his experiments because of species differences, or that other substances appear in these conditions, not tested by him, but similar in activity to methemoglobin in the acidotic dog. In this regard, Bywaters has claimed reproduction of the "crush" syndrome in acidotic rabbits by the injection of myoglobin (122).

On balance, the kidneys add to resistance against shock (140). They appear to participate in the general neurogenic vasoconstriction of the vascular system and also respond to an abnormal nonrenal pressor substance, secrete renin and react to its product, and reduce their excretion of water.[5]

The normal dog, in shock due to partially occluding limb tourniquets or hemorrhage, displays scanty dilute urine, sharply reduced renal blood flow and glomerular filtration rate, with variable changes in filtration fraction (104, 141). Page and his coworkers have investigated the validity of the use of diodrast clearance in shock as a measure of effective plasma flow (104, 141). Plasma diodrast extraction ratio in the explanted kidney is unchanged until the occluding torniquet is released or the severe hemorrhage induced. Then, it falls considerably and unpredictably. As a consequence, measurements of renal blood flow in shock based on clearances must be interpreted with caution. Corcoran & Page point to two causes for discrepancy between diodrast clearance and effective renal plasma flow (141). At low levels of blood pressure, filtration and diodrast secretion probably cease in more and more nephrons, while blood continues to flow through them. Thus at 50 to 60 mg. Hg, diodrast clearance becomes uninterpretable; between 60 to 70 mg. Hg, it understates renal plasma flow. Filtration fraction, being dependent on plasma flow, reflects its errors. Inulin clearance does not suffer correspondingly from hypotension as a measure of glomerular filtration rate as judged by the constancy of its equality to creatinine clearance. When sudden changes in renal function, as after transfusion, occur in this critical hypotensive zone (they are less likely to arise at higher pressures, where

[5] No doubt other effects occur but they are not included in the material under review.

kidney function is vigorous), spurious values for diodrast clearance and negative diodrast extraction ratios can arise. This is explained by reference to extra diodrast secreted but not excreted by non-filtering nephrons, and to diodrast mobilized from interstitial fluid.

The cause of the observed fall in dog's renal plasma flow during shock is analyzed with considerable care. Anesthesia is excluded (104, 133). Hypotension, while partly responsible (141), is not the prime factor in early shock, nor is decreased blood volume, since transfusion to maintain blood pressure fails to prevent a fall in blood flow but shows a tendency to lower filtration fraction and increase urine output (104). Computation of changes in renal resistance to blood flow, taking account of reduced blood pressure and the changes in viscosity caused by rise in the hematocrit, shows that renal resistance is definitely increased and that the increase in viscosity due to erythremia is etiologically of secondary importance. Splenectomy to abolish erythremia, at least temporarily, confirms this finding. By analyzing resistance into its pre- and postglomerular components, it is shown that vasoconstriction of both afferent and efferent glomerular vessels probably occurs, with efferent vasoconstriction predominating (104).

Whether the renal vasoconstriction is partially neurogenic in the dog is not altogether certain. Corcoran, Taylor & Page report that reduction in renal blood flow during shock due to tourniquets is less pronounced if the kidneys have been denervated (104). Corcoran & Page find no difference, however, in shock caused by severe hemorrhage (141). In man, species differences may favor neurogenic renal reflexes and it must be remembered that the use of anesthesia in experimental animals tends to exclude painful stimuli, often a factor in human shock. Opinion in this question must continue to be reserved. Page and his co-workers conclude that renal vasoconstriction in experimental shock is in good part humoral in origin (95, 104, 141).

In thirty-five cases of shock in man, where clearance methods were used as estimates of effective plasma flow and glomerular filtration rate, both were considerably reduced, along with urine output, in all cases of shock and roughly proportional to its severity (142). The decreases are greater than can be explained by hypotension alone, and exceed that for the rest of the circulation, as shown by increase in the renal fraction of the subnormal cardiac

output. Clearances are lowest with lowest blood pH, but they are probably not directly related: renal ischemia no doubt increases acidosis by failure of the kidneys to excrete enough acid. Acute alcoholism and oliguria as complications of shock depress both filtration fraction and renal flow, probably by promoting continued systemic vasodilation. Renal vasoconstriction occurs in man during shock, as it does in the dog.

Following transfusion during shock in man and in the dog, renal plasma flow and glomerular filtration rate increase with rising blood pressure, but disproportionately, so that filtration fraction tends to rise. Later, plasma flow through the kidneys usually shows a progressive fall, affecting the filtration fraction, and becomes progressively less responsive to repeated transfusion, a fact indicating increasing concentration of plasma vasoconstrictor substance (141). Dogs with denervated kidneys do not show the "overshooting" of diodrast clearance seen in normal dogs after transfusion; the changes in their renal dynamics correspond to those in the innervated animal, but are somewhat slowed and incomplete. Possibly the denervated kidneys exhibit early vasoconstriction secondary to sensitivity to an increase in circulating epinephrine (141).

The nature of the pressor substances found in shock is of considerable interest. While epinephrine is active, but less effective than normally (143), other pressor substances are also present. Increase in circulating renin and angiotonin are reported in dogs after hemorrhage (144). Renin substrate (hypertensinogen), while at first increased, is later reduced along with angiotonin in dogs shocked by hemorrhage, but not if they have been nephrectomized (144, 145). It appears that the substrate is used up by the increased renin faster than it is formed. Angiotonin (hypertensin) refractoriness can also develop, after central nervous system injury in dogs and cats (145), and also after severe hemorrhage (143, 144, 145).

Page shows that a vasoconstrictor substance, not histamine, and different from those mentioned and different from the vasoconstrictors in shed blood and blood in human or canine hypertension, is formed in shock due to intestinal stripping, burns (95), hemorrhage, and tourniquets (104). It appears fairly late in shock and is not affected by prior renal denervation, nephrectomy, adrenalectomy, and low spinal destruction.

Warburg respiration studies on liver slices from fasted rats

shocked by hemorrhage show little depression of respiration (146). Exposure of normal kidney slices to nitrogen for fifteen to sixty minutes causes as much respiratory depression as occurs in liver slices,—the degree being more than that occurring in shock. Unlike the liver, kidney slices show marked recovery of respiration after nitrogen exposure in the presence of glucose.

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The war has curtailed research and it is difficult or impossible to obtain many of the foreign journals. Yet a listing of the literature on blood from July 1943 to July 1944 alone would far exceed the space allotted to this review. The omission of certain topics or papers was dictated rather by space limitations than importance of the work. In reporting work which was a continuation of previous investigations, it was usually impossible to give the background. Therefore, the worker quoted in the period covered does not necessarily have priority on the conclusions he reached. The omission or inclusion of authors' names in the text was dictated by readability, and not by the relative importance of the work.

Reviews on Blood

During the year under consideration valuable reviews have appeared on various aspects of blood: blood in general (1 to 7), coagulation (8, 9, 10), transfusion and blood substitutes (11 to 16), blood banks (17, 18) blood groups (19, 20), pernicious anemia (21, 22), bone marrow (23), hemolytic anemias (24), hemolysis (25), plasma proteins (26, 27, 28), and white blood cells (5, 29, 30).

Coagulation

Prothrombin and vitamin K.—According to Quick (31, 32) prothrombin appears to be a complex of calcium plus two components: prothrombin A, which disappears from oxalated stored blood, and prothrombin B, which disappears from dicumarol blood. Mixing the two restores the prothrombin level, presumably because component B remains in oxalated plasma and A in dicumarol plasma.

In the rat, the role of the cecum in vitamin K synthesis is emphasized by Wakim *et al.* (33, 34) who found that neither succinylsulfathiazole nor cecectomy appreciably lowered the plasma prothrombin content, while a combination caused severe or fatal hypoprothrombinemia. However, Kornberg *et al.* (35) administer-

ing various sulfonamides to rats produced hemorrhagic conditions which could be corrected by vitamin K.

Hypoprothrombinemia produced in chicks by a K-deficient diet involves no hepatic histopathology (36). Shemiakin *et al.* (37) contend that the antihemorrhagic action of vitamin K and its synthetic analogues is due to degradation to phthalic acid, which is the true carrier of biological activity. However, Dam (38) finds phthalic acid and its diethyl ester to be inactive and therefore not responsible for the prothrombinogenic action of vitamin K.

Conditions favoring hypoprothrombinemia were studied, including biliary obstruction and liver disease (39, 40), scurvy (41) [although Link *et al.* (42) do not ascribe the delayed clotting in vitamin C deficiency to hypoprothrombinemia], blood dyscrasias (43), warm environmental temperatures and climates (44), the premenstrual period (45), and hemorrhagic disease of the newborn (46 to 49). The hypoprothrombinemia occurring frequently in tuberculosis, especially when there is hemoptysis, can be corrected by vitamin K, but there is no influence on the hemoptysis itself (50, 51).

Anticoagulants: dicumarol and heparin.—Link *et al.* (52) report that 3,3′-methylenebis(4-hydroxycoumarin), called dicumarol, is the most potent anticoagulant of the 4-hydroxycoumarin class. Although the salicylates have a similar prothrombinogenic effect (52, 53) it is doubtful that dicumarol acts *in vivo* through conversion to salicylic acid (54). Studies are reported on dogs in which dicumarol prolongs the prothrombin time (55) and reduces the incidence of thrombi induced by injection of sclerosing agents (56). Barker (57) finds in 624 surgical patients that dicumarol therapy significantly reduces the incidence of postoperative thrombosis and fatal embolism. The complication of hemorrhage from the hypoprothrombinemia of dicumarol administration (58) can be controlled by intravenous vitamin K (59, 60).

Heparin continues to be employed clinically to prevent thrombus formation (61, 62, 63). A combination of heparin and dicumarol is recommended (55, 64). De Takats (61) has devised a simple test for heparin sensitivity to permit making allowances for great individual variations when heparin is employed therapeutically.

Huggins *et al.* (65) ascribe the fluidity of menstrual blood not to an anticoagulant, but to the action of a fibrinolytic enzyme found in menstrual blood and uterine fluid. Tocantins (66, 67) re-

ports further on the antithromboplastin in normal blood and tissues and its role in hemophilia.

Natural Blood Substitutes

The problem of shock and the general question of blood substitutes in its therapy are beyond the scope of this review on blood. There is fair agreement that the best blood substitutes are such natural products as whole blood, plasma, serum, serum albumin or cell suspensions. However, research on the artificial substitutes has important practical applications and will continue to contribute to our understanding of shock and related phenomena.

Transfusion of whole blood.—The widely used sodium citrate-glucose mixture for preserving blood has disadvantages which are corrected by adding citric acid (68). Ross *et al.* (69), using a "tagged iron" technique, found that the survival time of transfused red cells was markedly reduced when the donors' citrated blood was stored more than six days. Experiments employing the Wiener technique failed to confirm this damage by storage (70). Bruneau & Graham (71) reported that heparinized, transfused blood was tolerated by recipient dogs better than was citrated blood. However, the present high cost of heparin would seem prohibitive in the preservation of blood and plasma. Steinberg (72) describes a new, inexpensive anticoagulant, a resin which adsorbs calcium. Jensen (73) recommends that sulfonamides be employed for the suppression of bacterial growth in stored blood. It has been possible to freeze human blood rapidly and subsequently thaw rapidly with minimal hemolysis, although efforts to dry whole blood from the frozen state were not successful (74).

Technical errors in blood typing amount to 1.0 to 7.1 per cent (75), so that no health record identification tag of any individual in the service may be assumed to carry the correct blood group (76). Some typing errors might be avoided by the employment of the very potent typing sera described by Witebsky *et al.* (77). There are procedures to neutralize anti-A and anti-B agglutinins in the plasma of O donor blood (78); but pooled type O blood, in which an occasional high titer of agglutinins is diluted, has repeatedly been found safe (79).

On the whole, the dangers involved in transfusion are remarkably few. Carlson (80) reports only 11 serious reactions in 3,388 transfusions from banked blood, even before the time of routine

Rh determinations. The dangers of circulatory overloading have been pointed out (81), although the danger apparently is not great in cases unassociated with cardiorespiratory disease (82). Allen *et al.* (83) found that massive postoperative transfusions were well tolerated and therapeutically valuable. Tocantins *et al.* (84) report further experiments on successful infusions into the bone marrow, which is an important technique when intravenous injections are difficult or impossible.

Drew (85), in a review of the development of blood banks in Russia, describes the successful use of placental blood and cadaver blood. Cadaver blood has also been employed in this country (86).

Plasma as a blood substitute.—While blood transfusion is a relatively safe procedure, reactions to plasma are far fewer (87). Although an occasional plasma from an individual donor may contain a sufficiently high titer of agglutinins to induce reactions (88), many studies (89, 90, 91) have shown that the pooling of plasma containing high titers from only one or a few individual donors reduces the titer to virtual insignificance. However, when the pools are small, from few donors, it may be desirable to use the four types of plasma in proportion to their frequency in the population (89).

Plasma, even in the liquid state, may be preserved for as long as a year and employed with safety (92).

Blood banks.—The remarkable organization of blood banks and their use during the London blitz is described by Vaughan (93), and the British army blood transfusion (actually, dried plasma) service is reported by Whitby (94); the latter states that the average hemoglobin level of the British population is now lower than before the war. The latter finding is also reported from Australia (95).

The experience of the war has tremendously stimulated the forming of blood banks for civilian use, not only for occasional peacetime catastrophes, but in the routine of hospital care. Details of the organization of the banks, including a plan for supplying rural physicians (96) are presented in a large number of papers only a few of which are cited in the bibliography (97 to 103).

Blood banks are supplying blood and plasma not only for substitution therapy in shock, hemorrhage, and related conditions but are increasingly serving as centers for collection and distribu-

tion of specific immune plasma and sera for the therapy of infectious diseases (89, 104).

Bovine serum.—Another of the naturally occurring, less artificial blood substitutes recently employed is despeciated bovine serum (105, 106, 107). Edwards (105) found it to be safe when administered rapidly and in large amounts after he had destroyed antibody action by heating to 72°C. and prevented coagulation of proteins by adding 0.2 per cent formaldehyde and ammonia. Heyl *et al.* (106) employed concentrated solutions of crystalline bovine albumin in man, although Dunphy & Gibson (107) concluded from animal experiments that concentrated solutions seemed to produce kidney and liver pathology, as contrasted with nontoxic unconcentrated or slightly diluted solutions.

The employment of bovine serum in man poses questions regarding the intramolecular changes attendant upon denaturation and the molecular basis of antigen-antibody reactions. Such problems have excited considerable interest in recent years. De Falco *et al.* (108) were unable to confirm the contention of Lewis (109) that brief treatment with alkalies destroys the antigenicity of protein isolated from bovine serum, but contend that the procedure simply alters the antigenicity somewhat. Pauling, Pressman & Campbell (110) would account for these phenomena in terms of their lattice theory of serological precipitation and agglutination. Wright & Pauling (111) contend that denaturation consists of an unwinding of polypeptide chains. Such unwinding may disturb the organization at the specific combining zone, in which case the immune response would be destroyed. If the unwinding should leave the combining zone of the molecule intact, the antibody might still retain its specific reactions. In opposition to the interpretations of the Pauling group, Erickson & Neurath (112) hold that "the difference between antibody globulin and normal globulin is not merely one of steric arrangement but probably one of amino acid composition."

Erythrocyte suspensions.—Tui and co-workers (113) emphasize the tremendous nutritional waste entailed in discarding cells in the preparation of plasma and suggest that the cells be reinfused into the donors. This restores the total plasma protein and the hematocrit to normal within forty-eight hours. The use of cell suspensions instead of whole blood conserves plasma for military purposes (114,

115) and meets a major civilian transfusion need in the anemias (116). It is well tolerated (116, 117, 118) and can be stored for as long as thirty days in glucose-citrate solution (119).

The Rh Factor

No other equally sharply circumscribed area in the field of blood seems to have evinced as much interest in the past year as has the role and nature of the Rh factor. There is nearly complete agreement with the earlier interpretations: erythroblastosis fetalis is produced in an infant because his Rh-positive cells are acted upon by anti-Rh agglutinins developed by the Rh-negative mother as a result of some of the fetal agglutinogens entering the maternal bloodstream and acting as antigens, with subsequent passage of the destructive antibodies back into the fetal circulation. Rh-positivity is transmitted as a Mendelian dominant. Also, repeated transfusions of Rh-positive blood into an Rh-negative recipient may eventually result in a reaction from the anti-Rh agglutinins developed by the recipient acting upon the cells of the Rh-positive donor.

Frequency.—The figures from 5,715 examinations made in Australia (120), England (121), and the United States (122) reveal that 84.3 per cent of the white population is Rh-positive, and 15.7 per cent Rh-negative; this corresponds well with previous studies which place these figures, in round numbers, at 85 per cent positive and 15 per cent negative. As a result it has been considered necessary to type for Rh factor those likely to receive repeated transfusions, those with a history of a transfusion reaction, obstetrical patients, babies born with jaundice and anemia, and all bloods drawn for transfusion (122). It is claimed by Ecker *et al.* (123) that the Rh antigen is present in all human red cells. In some (the Rh-negative) it is less sensitive, detectable only with appropriate anti-Rh sera.

Erythroblastosis fetalis.—Further interesting confirmations of the iso-immunization concept of erythroblastosis fetalis are supplied by Kariher (124) and Potter (125), each of whom reports fatal erythroblastosis fetalis in one of twins. In each case, the affected twin and the father were Rh-positive, the normal twin and the mother Rh-negative.

Stratton (126) has shown that the Rh factor makes its appearance early in pregnancy by demonstrating it in the blood of a 48

mm. embryo. It is also reported (127) that Rh-negative individuals who develop anti-Rh antibodies in pregnancy or by repeated transfusions remain immunized for years, if not permanently. Boorman *et al.* (128) have detected Rh group-specific substances in the tissues and in saliva. There is further confirmation of the finding of anti-Rh antibodies in the breast milk of mothers of erythroblastic infants by Witebsky *et al.* (129), Wiener *et al.* (130), and by Langley & Stratton (131). The maximum titer in breast milk occurs on the fifth day (129). The erythroblastic infant should receive neither transfusions nor breast milk from the mother.

Consequences of Rh reaction in utero.—Since the Rh-positivity of fetal blood is detectable very early in pregnancy (126) it is reasonable to expect that fetal damage from antibodies developed by the mother should occur *in utero.* Levine (132) and Schwartz & Levine (133) present evidence that some abortions and stillbirths might be related to the Rh factor. Van Dorsser and collaborators (134) studied the Rh type of 474 consecutive women entering the hospital and concluded that the pregnant Rh-negative woman is not more subject to fetal death than the Rh-positive woman in her first two or three pregnancies, but that in repeated pregnancies there is a significantly higher fetal mortality in Rh-negative women. Of interest in this connection is the description (135) of a severe hemolytic reaction following the transfusion of only 100 cc. of Rh-positive blood into an Rh-negative woman who had recently been delivered of a dead fetus.

In a small sampling of certain types of the feebleminded Cook (136) found a higher proportion of Rh-negative mothers and Rh-positive offspring than occurs in the general population, and conjectured whether intra-uterine hemolysis and cerebral anoxia of the fetus might be responsible.

Transfusions.—The importance of transfusing Rh-negative blood in erythroblastosis is underscored by observations in England (137) and the United States (138) that in transfusions of Rh-positive and Rh-negative bloods, the negative blood cells survived over eighty days, while the positive cells were destroyed within ten days by the erythroblastic recipient. Belkin & Wiener (139) describe an *in vitro* method of desensitizing anti-Rh serum by treating it with the stroma of Rh-positive red cells, an attack which may yield a new prophylactic and therapeutic weapon. The often-reported reactions occurring after repeated intragroup transfusions

(140) are said by Brown & Levine (141) to occur in Rh-negative recipients in 90 per cent of the cases, presumably because of the development of anti-Rh antibodies in the recipient consequent upon previous transfusion with Rh-positive blood.

Rh types.—Observations published in the past year by Race and associates (142, 143) in England and especially by Wiener and his collaborators (144 to 148) in this country have extended our knowledge of the sub-types of Rh-positive individuals. By employing three kinds of anti-Rh sera, it has been found that one of them (designated anti-Rh'_0 in Wiener's new terminology) agglutinates the cells of 87 per cent of the white population, another (anti-Rh′) agglutinates the cells of 70 per cent of the people, and the third (anti-Rh″) gives 30 per cent positive reactions. Utilizing these sera, it is found by Wiener (145, 146, 148) that white subjects fall phenotypically into eight Rh sub groups. These groups are inherited by means of a series of six allelic genes. The new terminology proposed by Wiener (148) is likely to introduce difficulties in comparing future with past findings.

Knowledge of the heredity of the Rh factor somewhat increases the extent to which exclusions can be made in medicolegal paternity cases (144). Racial differences are reported with regard to the Rh factor. Among Chinese there are only about 1 per cent Rh-negative individuals, while among the Negroes the Rh_0 type reaches a frequency of 40 per cent (145).

Unsolved problems of the Rh factor.—Although typical cases of erythroblastosis fetalis or Rh reactions after repeated transfusions fit the theory perfectly, troublesome questions still remain. Why should erythroblastosis fetalis result from maternal-fetal Rh incompatibilities when there is seldom if ever an erythroblastosis fetalis from incompatibility of the A and B substances (128)? Or may some unexplained cases be accounted for by A and B antigens (149)? What other explanation can be offered for the occurrence of erythroblastosis fetalis in infants with Rh-positive mothers (141, 149 to 152)? Why cannot anti-Rh agglutinins be detected in the sera of some mothers of erythroblastic offspring (141, 149)? Why is there often a poor correlation between the anti-Rh agglutinin titer of the mother, and the severity of the erythroblastosis fetalis in the infant (152, 153, 154)? Why is there less erythroblastosis fetalis than would be expected on the basis of the distribution of Rh genes in the population (154, 155)? Why is erythroblastosis

fetalis more common in later than in earlier pregnancies (149)? Why is hemolysis sometimes delayed for some time after birth (156, 157)? Successful attempts to account for some of these findings have been made (155, 158). Answers to other questions may eventually be supplied when there is further knowledge of the factors controlling passage of Rh agglutinogens and Rh agglutinins across the placenta (154).

The Role of Fat Ingestion in Blood Destruction

Johnson, Freeman & Longini (159) have reviewed the evidence, derived mainly from experiments performed at the University of Chicago since 1938, which lead to the concept that fat ingestion contributes materially to the daily destruction of red blood cells in normal man, and may play a role in the etiology of pernicious anemia. It has been shown that some fatty acids and soaps are absorbed as such, having escaped resynthesis into neutral fat. Some if not all of these materials enter the lacteals and thoracic duct. They are detectable in thoracic duct lymph in quantities sufficient to account for its hemolytic action.

Such determinations are made by chemical analysis of the lymph, which is a more direct procedure than the chylomicrographic method employed by Frazer and co-workers, who conclude (160, 161) that fatty acids are absorbed into the portal system and that neutral fat is absorbed into the lacteals.

The Chicago investigators (162) conclude that the following safeguards protect against hemolytic fatty acid or soap entering the blood stream too rapidly or in too great amounts. A high fat meal tends to cause vomiting; the emptying time of the stomach is longer after a fat meal than after meals rich in carbohydrate or protein; during absorption most of the injurious fatty acids and soaps may be resynthesized into harmless neutral fat; the unresynthesized hemolytic substances entering the lacteals are diluted in the thoracic duct; and, they enter the blood stream slowly and immediately mix in the subclavian vein and the heart with blood from all the body instead of mixing initially with only the blood in the intestinal capillaries.

Despite these protective mechanisms, after a fat meal the circulating red blood cells become exposed to a sufficient quantity of the hemolytic agents to increase the rate of normal daily red cell destruction. In dogs (163, 164) and also, as shown by Holt *et al.*

in human infants (165, 166), the daily excretion of the degradation products of hemoglobin is greater on a high than on a low fat diet. Furthermore, dogs' red blood cells exposed to lipemic serum *in vitro* are rendered immediately more fragile (162, 167). These experiments suggest that red cells are destroyed *in vivo* very soon after the products of fat digestion enter the blood stream. Actually there is an increased bilirubin excretion in anesthetized dogs within an hour or two after intravenous injection of small quantities of fatty acid or soap (168).

Although red cell destruction is greater on a high than on a low fat diet, the normal bone marrow is capable of replacing the extra losses, so that no anemia results. Also, dogs kept anemic by repeated bleedings recover as quickly on a high as on a low fat diet (169). However, autopsy reveals a greater amount of active hematopoietic tissue in the bone marrows of the fat-fed dogs. This indicates that, although recovery from hemorrhage is not appreciably impaired by a high fat diet, the bone marrow of fat-fed animals is taxed more than the marrow of anemic dogs fed a low fat diet. At another laboratory, Davis (169a) was able to produce marked decreases in erythrocyte counts in 4 dogs by feeding lard and choline simultaneously. Discontinuation of fat feeding resulted in rapid return to normal. His interpretation of these findings is that the choline prevented the bone marrow from compensating for the increased red cell destruction incident to the high fat diet.

Extension of some of these studies to human subjects has shown that the erythrocytes of normal man are rendered more susceptible to hypotonic hemolysis through exposure to lipemic serum (159). Erythrocytes in various anemias were studied for the reason well stated by Ponder (25):

> If the hemolytic system exists normally, there are always the possibilities (a) that the concentration of lysin will increase and . . . (b) that in the presence of an accelerator or because of the reduction in the concentration of an inhibitor the lysin will become more effective than it was previously.

In untreated pernicious anemia (159), lipemic serum produced not only an increased erythrocyte fragility but also actual hemolysis, when lipemic serum and red cells of the same individual were mixed. By contrast, lipemic serum of adequately treated pernicious anemia patients and of normal man produced only increased fragility but no actual hemolysis of their own red blood cells.

Further experiments indicated that this effect is at least partly attributable to an erythrocyte abnormality in pernicious anemia. On exposure to normal human lipemic serum, the erythrocytes of pernicious anemia patients were rendered more susceptible to hypotonic hemolysis than were the red cells of normal individuals, certain anemias other than pernicious anemia, and treated pernicious anemia (170).

In the light of these findings, it is of interest that Dunham & Brunschwig (171) produced a severe secondary anemia by injecting emulsified fat intravenously in dogs.

Pernicious Anemia

The anemias will be presented very briefly, because of the coverage of this subject in the excellent "annual reviews" on blood by Bethell, Sturgis, Mallery, and their collaborators in 1943 and 1944 (1 to 4). The important role of the vitamins in anemia is also omitted (172 to 176).

The effects of the war on the blood picture of Englishmen was mentioned earlier (94). In unoccupied France anemia is almost universal. Much of this anemia is hyperchromic, perhaps from inadequate intake of the extrinsic factor (177).

Hemmeler (178) ascribes the high serum iron content in pernicious anemia partly to hemolysis and notes that after liver therapy, the serum iron content drops, possibly because of a reduction in hemolysis.

In an investigation of the occurrence of relapses, Schwartz *et al.* (179) note no correlation of this with the time since cessation of therapy (usually through neglect), with age, sex, race, duration of previous treatment, or total amount of liver employed. The behavior in remissions is highly individualized. These investigators also report a far lower incidence of pernicious anemia in negroes than in whites (180) and the occurrence of an atypical febrile form of pernicious anemia in young colored and white adults (181).

The relationship of pernicious anemia to the stomach remains further to be clarified. Lahey & Marshall (182) found no pernicious anemia in seventy-three cases of total gastrectomy. Coller and coworkers (183) report the same results. Whether these findings may be due to a failure to survive sufficiently long to develop pernicious anemia or to an elaboration of the intrinsic factor elsewhere is un-

known (47). Extremely few instances of anemia of the pernicious type have been reported following gastric resection (184). Jacobson & Palmer (185) report a delayed gastric emptying time in severe pernicious anemia, contrary to the general belief.

Evidence for the presence of substances influencing biliary function in liver preparations is presented by Colvin (186) and by Hill & Hausmann (187). Last & Last (188) failed to confirm previous reports of a pernicious-like anemia in internal bile fistula dogs, which had been suggested as suitable animals for bioassay of liver preparations. A series of interesting experiments by Copenhaver (189) possibly bearing upon the role of liver in pernicious anemia revealed that removal of the liver anlage in *Amblystoma* embryos was later followed by an anemia unless the liver tissue was transplanted to another region. There are further reports of varying degrees of acquired intolerance or sensitivity to liver preparations (190 to 194).

Hematopoiesis

The bone marrow.—In a continuation of former studies on the proliferation of myeloid and lymphoid blood cells from injection of fractions from the urine of leukemic patients, Miller & Turner (195) conclude that two specific substances are involved in the normal formation of lymphoid and of myeloid cells, and that imbalances in the concentrations of these in the body produce leukemia. From experiments on the control of leukopenia in rats it is concluded that liver contains a substance of importance to white cell formation in the rat (196). Certain other liver fractions can also induce lesions resembling those of Hodgkin's disease (197). Menkin (198 to 201) reports further on the role of the leucocytosis-promoting and other factors derived from inflammatory exudates. Among the numerous reports on agranulocytosis, mainly from the sulfonamide drugs, the suggestion is revived that dietary deficiencies may explain the marked sensitivity of some individuals to these drugs (202).

De Bruyn (203) was unable to confirm previous reports that lymphoblasts and myeloblasts can be differentiated in tissue cultures by differences in their manners of locomotion. Limarzi attempted to deduce hematopoietic lineages from the differential action of arsenic upon megaloblasts and pronormoblasts (204) and

from sternal marrow studies (205). Marrow punctures are widely used for histological studies in animals (206) and in man (205, 207). Regarding these and other marrow studies (208, 209, 210), Osgood & Seaman (23) might be quoted, from their excellent review:

> It was hoped . . . that . . . specific recommendations could be made as to normal standards for aspirated marrow. It is apparent from the data presented that this must await further studies and a more general agreement on the technic of marrow aspiration and the handling of the material after aspiration, and especially on the acceptance of more uniform criteria of cell identification and nomenclature.

Iron in erythropoiesis.—Although liver iron concentration is not significantly different in normal and scorbutic rats, there is a marked decrease in plasma iron in scurvy (211). The intravenous administration of ascorbic acid increases the iron in serum (212). Whether vitamin C is involved in the transport of iron from liver to bone marrow (211) or the alimentary absorption of iron (212, 213) is not clear. In scurvy, the bone marrow displays reduced erythropoiesis (214). The common anemia in children in England responds well to increases in dietary iron without ascorbic acid supplements (215, 216).

Exploitation of the technique employing radioactive elements for metabolic studies has been productive in blood studies and especially in problems of iron metabolism. Hahn (217) has employed it to check a new and simple method for determining the total mass of red cells in the body. Sheline and co-workers (218) and Hahn *et al.* (219) report that an anemic animal absorbs much more iron than the nonanemic dog, after the body stores of iron have been depleted. Variations in amount of iron administered do not influence the quantity absorbed nor is a positive iron balance necessarily accompanied by increased hemoglobin values (220). Ordinary doses of iron cause some "mucosa block," diminishing the absorption of radio-iron fed one to six hours later. A mucosal acceptor, similar to splenic apoferritin, is postulated as regulating intestinal absorption (219, 220). Ferritin (221), or a related substance (222), is probably the chief storage form of iron in the body.

Iron phytate, recently used extensively in the fortification of flour, is a poor source of iron, apparently because of poor absorption (223, 224, 225). Sodium iron pyrophosphate is likewise less effective than ferrous or ferric sulphate in enriched bread (226,

227). Ferrous sulphate is more effectively utilized than ferric ammonium citrate (228).

Smith & Medlicott (229) found that milk anemic rats responded to copper administration, suggesting that copper stimulates hematopoiesis apart from catalyzing the introduction of iron into the hemoglobin molecule. Further evidence for the role of manganese in erythropoiesis was also presented (230).

Hemolysis[2]

Ponder (25, 231) discusses certain similarities between the inhibitory effect of plasma or serum on hemolysis by saponin and similar lysins and the mode of action of other inhibitors and accelerators of hemolysis. Hemolysins are concluded to act by reacting with cell membrane components. Accelerators or inhibitors react with the same substance, increasing or decreasing the effectiveness of the lysin. Further evidence is presented that certain red cell changes formerly attributed to lysolecithin action may be explained otherwise, and that this agent is not responsible for congenital hemolytic icterus (232). Citrate-glucose preservatives for blood inhibit lysolecithin hemolysis (233).

Lee & Tsai (234, 235, 236) extended to other species combinations their finding that cholesterol inhibits the hemolytic action of normal dog serum on normal rabbit cells. The inhibition is due to inactivation of complement (234). The immunization of dogs with rabbit cells causes the development of an anticholesterol factor which increases the hemolytic effectiveness of the immune dog serum (235). Serum protects rabbit cells from hemolysis by dog serum not only by the anti-complementary action of cholesterol and allied substances, but by a factor which inhibits the sensitization of rabbit cells by dog serum (236).

Ballentine (237) presents evidence that species differences in permeability of erythrocytes cannot be related to differences in the amino acid composition of stromatin, the protein of stroma. Roy (238) correlates species differences in fragility to hypotonic salt solutions with differences in size of cells: fragility varies inversely with the average diameter. This author also concludes that alterations in surface tension play only a minor role in hemolysis (239).

[2] See also discussion on the role of fat ingestion in blood destruction pp. 373 to 375.

Ether is said not to hemolyze by extracting membrane lipoids unless it is present in sufficient excess to form a separate phase (240).

The hemoglobinuria following thermal burns is attributed by Ham *et al.* (241) to hemolysis by heat at the site of the burn. The lysins found in human urine have been identified as hemolytic bacteria (242). Excellent reviews have appeared on subjects related to hemolysis: the hemolytic anemias (243), cold hemagglutination (244), and hemoglobinemia (245).

Plasma Proteins

Postoperative hypoproteinemia occurs most frequently in bleeding peptic ulcers, gastrointestinal malignancy, bowel obstruction, and intestinal fistulas (246). Rhoads *et al.* (247) ascribe the hypoproteinemia in malignancy to a defective fabrication of proteins due to the presence of the tumor, and not to dietary deficiency or blood loss, and report successful prevention of low plasma proteins by the preoperative ingestion of a high protein diet (248). However, the diet seems not to influence the rate of regeneration of plasma protein after a single severe hemorrhage (249).

There has been continued wide interest in the replacement of dietary protein by the injection of substitutes of protein derivation. Hypoproteinemia can be at least partially corrected by the injection of amino acid mixtures in dogs (250, 251, 252) and in man (253, 254).

Further work on the utilization of parenteral amino acids (255) and proteins (256) yielded results in accord with the conclusion reached by Elman (28):

> Review of the literature through 1943 reveals sufficient evidence of the fact that nitrogen balance may be achieved both in animals and man by the intravenous . . . injection of all the essential amino acids or certain protein hydrolysates.

The hepatic origin of plasma proteins is further supported by the occurrence of hypoproteinemia in cirrhosis of the liver (257, 258) liver damage by carbon tetrachloride (259, 260), and hepatectomy (261). In these studies there is general agreement that a reduction in the albumin fraction is responsible for the low plasma proteins. The globulin fraction is little changed or even increased, this fact supporting the concept of extrahepatic formation of serum globulin (258 to 262).

Hyperglobulinemia appears principally in diseases involving the bone marrow or liver, in chronic infections, and dehydration, according to Kagan (263) who believes that his clinical data support the theory of the formation of globulin by the plasma cells and the reticulo-endothelial system. Beeson & Miller (264) ascribe the higher incidence of hyperglobulinemia in negroes than in whites to the higher incidence of lymphogranuloma venereum in negroes. Serum globulin, and to a lesser extent serum albumin, increase in quantity with the age of infants and children (265).

The important implications of protein-inadequate diets for increased susceptibility to infectious disease is further emphasized by Cannon and collaborators (266) who report that experimental hypoproteinemia renders rabbits less capable of producing antibacterial agglutinins.

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THE LYMPHATIC SYSTEM

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This paper deals with publications upon the lymph, lymphatics, lymph nodes, and lymphocytes following as directly as possible upon that of McMaster (1) in 1943. His review covered available material approximately between 1940 and September, 1942. In dealing with another two-year period, during which the war has effectively checked most of the fundamental research upon the lymphatic system, it has appeared best to divide the subject quite simply rather than to follow the more elaborate arrangement of headings used by McMaster, for whom much more work was available for review.

Applied Anatomy

Freeman (2) has done a useful service for physiologists by carefully anatomizing the thoracic duct. He refers to the problem of the entrance of fat into the circulation after absorption from the intestine, pointing out that simple cannulation of the duct in the dog may not exclude lymphatic absorption, since the presence of small accessory connections with thoracic veins or branches crossing to the right duct may readily deliver fat to the blood by lymphatic pathways, though through unusual routes. Freeman made careful injections of the thoracic duct in twenty-five dogs anesthetized with pentobarbital. The results are summarized in Table I, showing the manner in which thoracic duct lymph could enter the circulation. In but eight instances did the lymph have access to

TABLE I*

Thoracic Ducts in Dogs

Group	Number of Animals
1. No branches	3
2. Divided left ducts	5
3. Branches to right side	8
4. Branches to azygos vein	5
5. Branches to right side and to azygos vein	4

* Freeman (2).

the blood through the thoracic duct alone. In thirteen dogs the thoracic duct and all branches were tied aseptically at the conventional point of entrance into the circulation. One animal died as a result of the operation. The remaining twelve recovered normally and were killed after periods up to 225 days. All "showed various types of lymphatico-venous communications which were probably enlargements of pathways normally present." Since all the connections found were in the neck or high in the thorax, Freeman suggests cannulation of the thoracic duct in the chest as the best way to collect intestinal lymph.

Allen (3) showed that the parietal tunica vaginalis of man possesses an extensive lymphatic plexus comparable to that of the parietal pleura. These lymphatics, arranged in superficial and deep layers, must be of importance for the removal of serous fluid from the endothelial-lined sac in which the testis lies. They drain into the same abdominoaortic nodes as do the lymphatics from the testis. Allen used material secured at autopsy within a few hours of death. The saccus vaginalis was punctured with a fine needle, washed out repeatedly with physiological saline to get rid of proteinized fluid, and then 5 cc. of India ink were injected, the opening closed, and the preparation massaged for five minutes, after which the ink was washed out and the material fixed in 10 per cent formalin for study.

Grinnell (4) examined the lymphatic and venous spread of rectal carcinoma. He utilized seventy-five specimens of the rectum and rectosigmoid removed at operation. All specimens were fixed and cleared by the Spalteholz method, and in every case the lymph nodes were eventually removed and sectioned. The number of nodes so found was surprisingly large, the average number being fifty-two. Some of these containing metastases were only 1 to 2 mm. in diameter. The lines of spread are described in some detail by Grinnell and are illustrated by diagrams.

Another somewhat incidental anatomical finding but important for physiologists is the verification by Warren & Drinker (5) of the fact that collection of lymph from the right lymphatic duct of dogs will provide practically the entire delivery of lymph from the heart and lungs. Since the duct can be cannulated outside the chest this procedure offers a useful method for studying lymphatic absorption from the lungs, a method of removing proteinized tran-

sudates and exudates of great practical interest. The work of Freeman (2) indicates that right duct lymph may also contain large additions from the intestine. It is, however, easy to check this possibility in experiments by injecting the blue dye T-1824 in a hind foot and then massaging the foot, leg, and abdomen. If connections between the thoracic duct and right duct exist they will be apparent in a matter of minutes, since the blue dye will flow rapidly up the thoracic duct and will color the right duct lymph. By clamping the thoracic duct the observer can be even more certain of the situation in regard to anastomoses. Muus, Hardenbergh & Drinker (6) found that the single way they could secure practically the complete lymph delivery from the hind legs of a dog was to open the abdomen and cannulate a large trunk lying along the aorta just below the receptaculum chyli. When this was done and other lymphatics in the neighborhood of the cannulation were ligatured, it was possible to secure a comparatively free flow of lymph from the legs if they were kept in mild passive motion. The tail, skin of the rump, genitalia, and rectum are also included in the drainage area, but in the anesthetized animal lacking motion or massage lymph delivery from these regions is insignificant. The preparation is the best so far used for obtaining large amounts of dog lymph uncontaminated by abdominal contributions.

A final relatively simple anatomical finding is that of Glenn, Muus & Drinker (7) who were able to collect lymph from the forelegs of calves by cannulating the draining lymphatics after they come together in a single large vessel just inside the shoulder of the animal. This preparation enabled them to secure very large amounts of lymph for chemical analysis. This preparation is fully described by the authors and is highly useful when a copious supply of lymph is essential.

Physiological and Biochemical Investigations

The interest in inflammatory exudates due to infections, grievous wounds, burns, and all the onslaughts of war has directed much attention to the composition and characteristics of such fluids. One of the difficulties in their study is the lack of something definite to use as a standard. Amongst the properties of exudates which have become important is their power to coagulate. Since

lymph from regions of inflammation can be collected from draining lymphatics, it presents the best source of uncontaminated inflammatory exudate. Amongst the normal data required for comparison with inflammatory lymph are estimates of the factors of coagulation. Brinkhous & Walker (8) collected lymph from normal dogs anesthetized with morphine and ether. They estimated the prothrombin and fibrinogen concentrations of thoracic duct, portal, and femoral lymph using plasma collected at the same time for comparison. They found prothrombin and fibrinogen in thoracic duct lymph in approximately one half the plasma concentrations. Prothrombin in liver lymph was about equal to that in plasma. In femoral lymph there was less than one tenth of the plasma concentration. These findings are fairly well in accord with the average percentage of protein found in lymph from the sources examined. In relation to these results it may be mentioned that lymph from seriously burned regions clots very ineffectively or not at all.

Warren, Peterson & Drinker (9) found it possible to cannulate the right lymphatic duct in dogs and thus collected a mixture of lung and cardiac lymph without opening the chest. Since it has been shown by Drinker, Warren, Maurer & McCarrell (10) that the heart produces lymph in accordance with the vigor of beat at the moment, it was necessary to show that cardiac output remained reasonably constant during the collection of right duct lymph so that changes occurring under different experimental conditions could be due to events in the lungs alone. It was readily shown that in animals breathing oxygen so as to exclude anoxia, the flow of lung lymph increased many times when inspiration was carried on against resistance. This was interesting evidence as to the effects of increased negative intrapulmonic pressure in inducing abnormal degrees of filtration from the lung capillaries into the parenchyma. Under artificial respiration held absolutely uniform it was found that when oxygen in the ventilating air was reduced to 10 per cent, lymph flow increased at once and immediately returned to normal when ventilation with pure oxygen was resumed.

The nature and significance of kidney lymph has had almost no attention, so that all observations in this lymphatic field command our interest. Sugarman, Friedman, Barrett & Addis (11) first summarize the slight amount of information in existence upon renal lymphatic drainage. Under pentobarbital anesthesia a kidney was

exposed through an abdominal incision. A small amount of T-1824 was then injected through the capsule for injection of the cervical lymphatics, and about 1 cm. into the parenchyma to inject the medullary vessels. Cervical lymphatics were ligated at the poles of the kidney and hilar lymphatics as they enter draining lymph nodes near the aorta. Cannulae were inserted and 0.5 to 1.0 cc. of lymph could be collected in twenty to forty minutes. Determinations of protein and urea concentrations were made upon blood and lymph. "Protein in the renal lymph varied from 0.4 to over 4.0 grams per 100 cc. The slower the lymph flow the greater in general was the protein concentration. . . . Urea in the renal lymph was always greater, often considerably greater, than the concentration of urea found in the plasma of the renal artery or vein." In a second paper Kaplan, Friedman & Kruger (12) asked two questions: "1, do the renal lymphatics drain only the larger collecting ducts of the kidney, thus accounting for the high urea content of its lymph, and 2, is renal lymph derived from the tubular reabsorbed fluid, the blood plasma or from both types of fluid." To answer the first question the glucose content of lymph from large collecting trunks in the hilus was compared with that of cervical vessels. Hilar lymph if derived from large collecting ducts should contain much urea and little or no glucose, whereas cervical lymph would have a glucose content corresponding with the blood. It was found that renal lymph, while having a lower glucose content than cervical lymph, still contained so much glucose as to indicate it is not derived solely from fluid in the large collecting ducts of the kidney. To answer the second question, as to whether renal lymph represented fluid absorbed from the tubules or directly from the plasma or from both sources, the inulin content of renal lymph during intravenous infusion of inulin was compared with that of cervical lymph and plasma. The renal lymph contained considerable inulin though less than cervical lymph. If derived from tubular reabsorbed fluid the inulin concentration would have been negligible. It is thus reasonable to assume that renal lymph is derived from both plasma and reabsorbed fluid.

The effects of anesthesia upon cervical lymph flow were examined by Polderman, McCarrell & Beecher (13). They compared the lymph flow in dogs under general anesthesia by ether and by pentobarbital with the results gained under local anesthesia. The

nodding-head preparation of McCarrell (14) was employed in order to provide constant conditions for lymph production and movement. Four series of experiments were done: (*a*) local anesthesia by 1 per cent procaine hydrochloride followed by pentobarbital, 20 to 40 mg. per kilogram intravenously, and then ether; (*b*) local anesthesia followed by ether and then pentobarbital; (*c*) ether alone and pentobarbital alone; and (*d*) pentobarbital followed by ether. It was found that pentobarbital decreases lymph flow 50 per cent as compared with local anesthesia and that ether increases the flow a like amount. Other observations indicated that under barbiturate anesthesia fluid moved from the tissues into the blood, and under ether the reverse occurred. It is pointed out that most of the recent experimentation on lymph flow has been carried out under pentobarbital and that this may account for the apparently normal animals so often encountered, in which lymph flow is insignificant and lymph protein often surprisingly high. It is suggested that ether may be useful for increasing lymph production.

Crandall, Barker & Graham (15) had an unusual opportunity to study lymph flow from a patient with a thoracic duct fistula. A colored woman was shot in the neck on the left side. At operation the internal jugular vein was ligated above and below the wound. As the bullet was approached straw-colored fluid "welled up into the incision" and flowed steadily during and, since the wound was not closed completely, after the operation. When the patient began to eat the fluid became milky but was not bloody. The patient lost weight at the rate of about five pounds per week, and in four weeks the plasma protein was 3.5 per cent. A high protein diet was then given and though weight loss continued the blood protein rose to 4.6 per cent. One month and thirteen days after the injury the thoracic duct was ligated and the wound closed tightly. There was no evidence of further leakage. For two weeks the patient complained of abdominal cramps after eating, but recovered without other annoyance and gained sixteen pounds before discharge from the hospital. It seemed probable that the fistula was complete as attested by absence of lipemia following a fat meal, by the loss of weight, and by the abdominal cramps following ligation which indicated a slow opening of collaterals. Early in the experience average lymph flow was 0.93 ml. per minute or 1.38 ml. per kilogram of body weight per hour. Food, water, and abdominal massage all increased the rate. Maximum flow was 3.9 ml. per minute, and minimum 0.38 ml. The protein content of the lymph

was 3.19 to 5.28 per cent. Olive oil stained by Sudan IV and given by mouth appeared in the lymph one hour and twenty-seven minutes after administration. The paper contains many other observations and is a unique contribution to the physiology of the lymphatic system.

Reinhardt, Fishler & Chaikoff (16) injected an isotonic solution of sodium phosphate (Na_2HPO_4) containing 2 to 2.5 millicuries of radiophosphorus intraperitoneally in dogs which were bled to death twenty-seven to forty-eight hours later and the plasma containing radiophospholipid was collected. The object of the investigators was to ascertain whether or not tagged phospholipids passed from blood to lymph—whether the capillary membranes involved were permeable to plasma phospholipids. The thoracic duct was cannulated in another series of dogs and 90 to 100 cc. of the tagged phospholipid plasma were given intravenously. Phospholipid was found in the thoracic duct lymph within thirty-seven minutes after injection, and 9 to 20 per cent of the injected radiophospholipids that left the blood appeared in the thoracic duct lymph in three to six hours. Since the permeability of liver and intestinal capillaries is comparatively great it is regrettable that lymph was not collected from other vessels such as the cervical ducts at the same time.

Lee (17) was interested in lymph extravasation and lymph pressure after ligation of the thoracic duct in the chest. Cats were used in the experiments. After ligation chyle extravasated in the region of the cisterna chyli within forty-five minutes and spread retroperitoneally and between the leaves of the mesentery. Lee found mesenteric lymph pressures of 5.2 cm. of water, and pressures in intestinal lymphatic trunks between the cisterna and the large mesenteric lymph node of 1 cm. of water. When the thoracic duct was tied pressure in the intestinal lymphatic trunks rose to 63.5 cm. of water, but in the mesenteric lymphatics pressure did not change. Lee believed the large intestinal lymph node acted as a buffer. Under the same circumstances lymphocytes accumulated in the intestinal lymph vessels and passed through their walls to become deposited in masses resembling lymph nodes.

Lymphoid Tissue

Jordan & Robeson (18) splenectomized pigeons. These birds depend upon the spleen for the steady delivery of lymphocytes into the blood. When the spleen is gone, compensation for the loss of

lymphocytes is accomplished by the development of nodules of lymphoid tissue in the bone marrow. These become evident by the end of the third week following splenectomy and are maximally large and numerous by the sixth week. If subtotal splenectomy has been done the nodules disappear as the spleen regenerates. The authors discuss the significance of their findings in relation to hematopoiesis in general. Kindred (19) has performed an arduous histological and statistical task in attempting to get quantitative data to support or condemn the idea that lymphocytes in the bone marrow become hemocytoblasts, the ancestors of erythrocytes, and that steady entrance of lymphocytes into the bone marrow from the blood provides a sufficient number of stem cells to keep up the normal supply of erythrocytes. He made

> a quantitative study of the volume, number of cells per unit volume, percentage distribution of different types of cells, percentages of cells in mitosis, growth rate, and destruction of cells . . . on the bone marrow, spleen, thymus, lymph nodes and Peyer's patches of a group of eight young adult albino rats, 80 days of age and weighing about 200 gm. each. The data obtained were used as the bases for calculations of the average production per hour per 100 gm. of body weight of erythroid and myeloid cells and lymphocytes particularly, on mitosis cycles of 1 hour and of 30 minutes duration, respectively.

Kindred concluded that the myeloid populations of bone marrow and spleen could supply many more myeloid cells than are needed by the blood, but the erythroid population of the organs examined was insufficient unless reënforced constantly by lymphocytes from the blood which they are known to enter in greatly excessive numbers through the thoracic duct. Kindred thus presents evidence for the lymphocyte as the progenitor of the erythrocyte, based upon laborious quantitations, the accuracy of which the author of this review is entirely incapable of estimating. If correct, further evidence has been obtained upon that very elusive question, the function of the lymphocyte. Kingsbury (20) has made a prolonged study of the structure and development of the laryngeal tonsils in the cat in the hope of getting some clue as to their function. In this last he failed, but has provided a useful account of the appearance and growth of these nodular masses of lymphocytic tissue under the pharyngeal mucous membrane.

Turner & Hall (21) have examined an old and puzzling problem as to what happens when large masses of lymphoid tissue are re-

moved or destroyed. Do new nodes develop, or is compensation achieved by hypertrophy of fragments of nodes or of untouched lymphoid tissue? They utilized adult, male albino mice, and under ether anesthesia removed about one-half the lymphoid tissue of the adult mouse. It was estimated that ten days later the remaining lymph nodes had gained 46 per cent of their original weight. The nodes which increased in size were invariably central to the excised structures, a finding which suggested to the authors that something in the lymph entering a node maintains its size but is inactivated in the node and can have no influence on more central nodes. If the peripheral node is removed, more central nodes are reached by raw tissue lymph. The study does not indicate formation of entirely new nodes.

Murray & Broders (22) have reviewed and extended knowledge upon primary malignancy of lymph nodes. Their paper is cited but not reviewed since the material is essentially histological pathology.

Augustine (23) infected rats with *Trypanosoma lewisi.* Sixteen days later they were etherized, the chest opened, and bled from the heart by means of a syringe containing heparin. This blood was centrifuged and the sediment containing blood cells and many trypanosomes was injected into the peritoneal cavity of a normal rat. Two hours later this animal was killed by a blow on the head. The thoracic duct was then isolated and cannulated. Lymph flow continued freely for about twenty minutes. Lymph nodes in the line of drainage contained a few trypansomes in contrast to the large numbers in the lymph. It is evident that these highly motile organisms pass nodes readily and without causing the slightest reaction.

The Lymphocytes

Cruickshank (24) made intraperitoneal injections of suspensions of rat lymph nodes in rabbits and obtained a serum which after hemolysins were removed reduced circulating lymphocytes when given intraperitoneally to rats. The fall in lymphocytes lasted for a week, but they never were caused to disappear entirely and it was never possible to show that damage was done to lymphocytes in the lymph nodes or spleen, nor was there any evidence of proliferation of lymphoid tissue. The serum produced was apparently

specific for rat lymphocytes. Berman (25) has developed a method for staining dry films from cultures of lymphoid tissue and seems to have been successful in following degenerative transformations of the lymphocytes. Cruickshank (26) observed that the circulating lymphocytes in man and animals become fewer after severe operations and rise again during wound healing. It is suggested lymphocytes are transformed into fibroblasts.

Clinical Physiology of the Lymphatic System

As might be expected, work in the lymphatic field during the past few years has been more largely on clinical lines resulting from attention to war problems than upon the more fundamental questions already covered.

Burns.—Wood (27) burned dogs, anesthetized with ether, by means of red hot soldering irons. After some time the dogs were given pentobarbital and the thoracic duct cannulated. Thoracic duct lymph rendered incoagulable by heparin was injected intra-arterially into an albino rat. There was no depression of blood pressure and consequently lymph from the extensively burned areas apparently contained no toxin injurious to blood pressure.

Glenn, Peterson & Drinker (28) were led into the study of burns through a desire to find out how far lymphatics were blocked by coagulum in inflammatory foci, an idea advanced by Menkin (29) as important for localizing certain types of irritants. The simplest repeatable inflammatory reaction they could use seemed to be immersion of the foot of an anesthetized dog in boiling water for precise periods of time. When this was done for two minutes, a lymphatic draining the foot having been isolated previously, lymph flow soon occurred without massage or movement of the part, increased for about six hours, and then slowly diminished over twenty hours. Swelling was rapid and extreme, and evidently clotting of the burn exudate was not sufficient to cut off lymph drainage. When, however, the burned foot was infiltrated with tissue extract injected through the skin, coagulation became extensive and lymph drainage ceased promptly. The authors felt that sustained swelling in such burned parts depended to a great degree upon deposition of coagulated exudate which collected and held a maximum amount of water delivered to the tissues from injured blood capillaries. The less the formation of coagulum the less sustained swelling would be present and the less the inert ma-

terial which must be removed before healing could be complete. It was found that if the blood and body fluids were rendered absolutely incoagulable by a large intravenous injection of heparin, swelling of a burned foot was much less. Such tactics in a spreading inflammation due to infection might be disastrous, but in an initially sterile inflammation reduction of the coagulated exudate in the part would hasten healing and diminish deformity. Finally, the authors attempted to prevent shock and collapse in severely burned dogs by complete blocking of lymph drainage into the blood. This was not successful.

Following this experience, Glenn, Gilbert & Drinker (30) examined the physiological results of making a burn by hot water immersion and then preventing all swelling by promptly encasing the burned part in a rigid plaster of Paris dressing. The summary of their paper is as follows:

The authors take the position that the fundamental condition to be met in treating burns is increased capillary permeability. This results in reduction of blood volume which is met by intravenous injections of blood plasma. The local consequences of abnormal capillary leakage have not been properly appreciated and, therefore, have not been combated by physiological methods of treatment. These consequences are

1. Loss of plasma into the tissues surrounding the burn.
2. Swelling.
3. Coagulation of the plasma in and about the burned area, resulting in a mass of abnormal material which must be removed during healing and which provides culture medium for bacterial growth and induces extensive deformity through excessive formation of fibrous tissue.

The enclosure of the burned part in a plaster of Paris dressing prevents abnormal leakage from the injured capillaries, since the rigid plaster case by virtue of the incompressible watery medium between it and the blood vessels becomes, in fact, the capillary wall and thus meets the necessities of the situation physiologically.

Experiments are reported in which the feet of dogs were burned for varying periods by immersion in hot water. They were then enclosed in plaster; first, by casting the burned foot which was held deep in liquid plaster until setting occurred, and second, by the use of roller-plaster bandages.

It is shown that the blood flow through the burned feet treated by these methods remained excellent and that healing occurred more rapidly and with less deformity than could be obtained if capillary leakage was unrestrained, as is the case in the absence of a rigid enclosure of the part.

The physiological reasons for this success are analyzed and, at the conclusion, the reservations are listed which should be in the minds of clinicians when the closed-plaster technique is used in treating human burns.

In order to obtain large amounts of lymph for chemical analy-

sis, Glenn, Muus & Drinker (7) cannulated the final draining lymphatic in each foreleg of calves anesthetized with pentobarbital. They measured lymph flow and lymph protein before and after burning. In addition, non-protein nitrogen, urea, creatinine, creatine plus creatinine, and amino nitrogen were determined in normal lymph, lymph after burning, and in serum. The data, presented in a series of tables, fail to disclose any significant abnormalities in the amounts of these familiar compounds in lymph from burned regions. These negative results are, however, useful as normals for further work upon calves and for establishing the character of exudates from burns uncontaminated by infection.

Lymph from similar burns in calves was used by Perlmann, Glenn & Kaufman (31) for examinations and comparisons of the electrophoretic pattern in the lymph as representing the burn exudate and in the serum. The results were as follows:

Normal lymph has the same four electrophoretic components as are present in serum: albumin, α-, β-, and γ-globulin.

The pattern obtained from lymph derived from the burned tissue revealed the occurrence of an additional boundary, migrating with half the speed of the γ-globulin.

The changes found in serum indicated a slight decrease of the albumin:globulin ratio with an increase in the α-globulin fraction.

In a search for some sort of biological reaction which might identify burn exudates as containing a factor having definite effects on living tissue, Muus & Hardenbergh (32) measured the oxygen consumption of normal rat liver slices in serum and in lymph taken from the legs of calves before and after severe burns. Contrary to their expectations they found the oxygen consumption of this normal rat tissue as much as 41 per cent increased when compared with the effects of normal lymph. Serum before and after burning gave less consistent results, attributable no doubt to high dilution in the blood. The material, entirely unidentified, which caused the increase in metabolism of the burn lymph was found in ultrafiltrate from this fluid.

Since patients with extremely severe burns not infrequently become the victims of hyperpyrexia, Muus, Hardenbergh & Drinker (6) developed a method for collecting large amounts of lymph from the hind legs of dogs, and then made studies similar to the preceding but employed diaphragm muscle from normal rats as the test

material. Findings similar to those obtained for calf lymph upon liver slices—a decided increase in oxygen consumption due to something in the burned lymph—resulted.

Alrich & Lehman (33) burned the feet of anesthetized dogs by immersion in boiling water for thirty seconds and then confined them in a plaster of Paris casting at intervals of fifteen minutes to one hour following the burn. In many instances lymphatics draining the burned area were cannulated in order to follow the protein concentration of the exudate. It was found that plaster confinement decreases plasma loss from the circulation and diminishes local loss of tissue, but these favorable effects become less marked with delay in applying the dressing following the burn. Alrich (34) extended this work to an examination of lymph from the burned feet of dogs in relation to the possible presence of vasoconstrictor and vasodilator substances. He collected lymph from the normal and burned feet of anesthetized dogs and found, using the method of Landis, Wood & Guerrant (35) in which the ear of a rabbit is perfused and reduction or increase in outflow of the perfusate from the veins is used to indicate constriction or dilatation of the vessels in the part, that when he added lymph from a burned part to the perfusate, vasoconstriction occurred. This was not one of the vasoconstrictor substances characteristic of serum and associated with coagulation, since it was found in lymph from burned animals previously heparinized so that no coagulation could take place.

The search for toxic factors in burn exudates has been concerned particularly with attempts to find something which increases permeability of blood capillaries in unburned regions and so might be important for reduction of blood volume and the production of shock. Netsky & Leiter (36) anesthetized dogs with morphine and pentobarbital. Cervical lymphatic ducts and the thoracic duct were cannulated, and then the animals were burned by dipping them to the axillae in water at 72°C. for sixty seconds. Just prior to burning, horse serum, 2 ml. per kilogram, was injected intravenously. It was found by immunological methods that capillaries in non-burned areas (cervical lymph) became more permeable to horse protein immediately after burning. The authors make it clear that this finding is to be evaluated for exactly what it is, and not made to cover the broad question of capillary perme-

ability until more work is done. Cope & Moore (37) approached the problem in the same general way but used radioactive colloidal dyes, mainly T-1824 which apparently combines with albumin in the plasma as the injected substance to be looked for in the lymph from non-burned areas. They used dogs and collected lymph from leg and cervical lymphatics and from the thoracic ducts. As a result of extensive experiments it is reported that no increases in capillary permeability were found outside the burned area except in one dog which it is admitted was late in shock.

As a final paper relating to burns, Glenn (38) has summarized in a useful way much of the material cited in this review together with more explanatory discussion.

Surgical shock.—Katzenstein, Mylon & Winternitz (39) anesthetized dogs with pentobarbital and then applied tourniquets as high up as possible on both hind legs. These were tied tightly enough not only to occlude the circulation but to bruise the underlying tissues. After five hours the thoracic duct was exposed and cannulated, and the lymph collected in tubes containing heparin and immersed in an ice-salt mixture. After releasing the tourniquets the thoracic duct lymph became bloody. When this lymph was injected intravenously into smaller dogs it caused a decided fall in blood pressure in 50 per cent of the animals used.

Blalock (40) produced shock in twelve dogs utilizing a quantitative crush injury to one of the hind legs of dogs anesthetized by morphine and pentobarbital. He collected thoracic duct lymph beginning at the fourth hour of the application of the press, and continuing until the death of the animal which occurred from three to nineteen hours after pressure was released. Twenty-seven to 115 cc. of lymph were collected. Most of this material was injected into normal dogs and caused a fall in blood pressure in about half of the recipients. In another series of similarly anesthetized animals crush injury was caused by pounding the legs with a blunt instrument without causing fractures. Thoracic duct lymph from these animals was less potent in causing ill effects when injected into normal dogs. Blalock points out that application of the press caused ischemia in contrast to the situation in the second group of dogs.

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HEART

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Anatomy and Embryology

The incomplete nature of our knowledge of even the gross anatomy of the heart of certain common mammals is attested by a few papers devoted to the gross and neuroanatomic features of the hearts of certain animals.

The number, anatomic distribution, and functional importance of the major cardiac veins of the right side of the heart of the dog have been studied from the point of view of their drainage by Gregg, Shipley & Bidder (1). From 50 to 92 per cent of the blood flow of the right coronary artery is drained into the right atrium rather than through the thebesian vessels into the right ventricle as formerly was believed by most workers. In sixteen experiments the flow from the major anterior cardiac veins ranged from 8.5 to 26.5 c.c. per min. Nonidez (2) whose observations were made on the heart of the pup and of the rhesus monkey has found that in addition to the sinoatrial (S-A) and atrioventricular (A-V) nodes, there is a distinct main bundle of the impulse conducting system. This divides into right and left bundle branches which are composed of swollen fibers. These fibers connect at various levels with the musculature of the ventricles. In the pup they resemble the typical Purkinje fibers of the calf, sheep, and so forth, whereas in the monkey they are less differentiated. The sinoatrial and atrioventricular nodes are supplied by parasympathetic postganglionic fibers. The main bundle branches of the dog's heart lack parasympathetic nerve endings, but in the monkey these terminal fibers occur in the main bundle and also in the proximal portions of the right and left bundle branches. Parasympathetic nerve endings are absent in the ramifications of the bundle branches in the two species. The rich supply of parasympathetic nerves to the atrioventricular node as compared with that to the sinoatrial node may account, in the author's opinion, for the production of atrioventricular block by electrical stimulation and by drugs, such as morphine and digitalis. An anatomical basis was found for the

inotropic effect of the vagus nerve by the existence of parasympathetic nerve endings in the atrial and auricular musculature.

The gross anatomy and the specialized conducting tissue of the heart of the common hedgehog (*Erinaceus europaeus*) have certain interesting features which have been revealed by Walls (3). The opening of the inferior vena cava is guarded by right and left venous valves and the coronary sinus has a right valve only. Cartilage occurs in the fibrous skeleton of the base of the heart. There is a sinoatrial node, an atrioventricular node, and an atrioventricular bundle. All of the nerve cells in the heart are found in the atrial side of the coronary sulcus, as in man and certain other animals. The atria lack Purkinje tissue. The rate of the heart is about 300 beats per minute.

Lissák, Törö & Pásztor (4) reported that hearts of chicks, forty-eight hours old, grown in tissue culture for two to four weeks did not contain acetylcholine before or after being grown in tissue culture. Hearts of chicks three to sixteen days old contained acetylcholine in significant amounts but this was lost after two to three weeks of culturing. At the same time all cardiac nervous tissue disappeared. When nervous tissue was implanted next to the hearts of chicks forty-eight hours old, the nervous tissue grew into the heart and subsequently the heart muscle contained acetylcholine. Electrocardiograms resembling those from the whole heart of chick and rat embryos were obtained from cardiac fragments by Szepsenwol & Odoriz (5) with a Gross oscillograph. The wisdom of designating the deflections produced by cardiac fragments in general and atrial fragments in particular by the letters, QRS-T, is questionable in view of the long association of these letters with a definite sequence in the beat of the whole heart.

Metabolism and Cardiodynamics

The results of two researches concerned with the question of tolerance of animals to anoxia have been published during the year. Lorber & Evans (6) working with the completely isolated heart of the cat concluded that the myocardium could not be regarded as the limiting factor in the tolerance of the intact animal to anoxia since the isolated heart withstood, without depressant effects, oxygen tensions much less than those tolerated by the intact animal. Increases in the output of the isolated heart of purely cardiac origin were seen only when carbon dioxide was absent from the venti-

lating gas. The effect was accounted for on the basis of changes in pH and was regarded as a systemic artefact rather than evidence of a direct stimulating effect of a low oxygen tension on the heart muscle. Randall (7) using intact dogs found that the blood pressure made a good but rarely complete recovery from the sudden crisis caused by anoxemic anoxia, when the animals were returned to atmospheric air. After six to twelve hours circulatory failure developed in most instances which was thought to be of peripheral origin since the electrocardiograms did not indicate failure of the myocardium. However, electrocardiographic changes that occurred during sustained anoxia suggested that the response of the myocardium is important in determining tolerance to lack of oxygen. That long continued exposure (three days or more) of cats to an atmosphere deficient in oxygen (4 to 5 per cent) has been demonstrated by Dearing, Barnes & Essex (8) to be capable of causing degenerative changes in the myocardium. The lesions which were more easily produced in old than in young animals were focal in distribution and most prominent in the papillary muscle and in the wall of the left ventricle. Smith & Wilson (9) have observed that spontaneous atrial fibrillation can readily be induced in the hearts of dogs by vagal stimulation or by injections of acetyl-β-methylcholine (mecholyl) if the hearts are anoxic. An observation of fundamental significance has been made by Lorber, Hemingway & Nier (10) on the assimilation of carbon dioxide by the completely isolated mammalian heart. With the hearts of cats, it has been shown that the carbon dixoide can be incorporated into the glycogen molecule of the heart muscle as well as into that of the liver. Similar results were obtained with and without the addition of insulin. These observations supported the conclusion that cardiac glycogen is constantly being broken down and reconstituted.

Complete rest with sedation by morphine has long been an accepted procedure in the treatment of coronary occlusion but in order to reduce the activity of the patient still more Buchbinder (11) has suggested continuous deep sleep induced by intravenous administration of barbiturates for the early stages of acute coronary occlusion and myocardial infarction. He reported encouraging results in one case. Although the heart may be benefited by such treatment, one must wonder whether the patient might be saved from immediate death from acute coronary occlusion only to succumb later to pneumonia.

Müller (12) has considered the pulse rate as an index of metabolic exchange and fatigability of working muscle. In his experiments the oxygen intake was kept constant but the rate of work was changed. From experiments done under these conditions he accounted for decreased pulse rate on the basis of peripheral changes and not on training of the heart because training of the muscles of the arms did not result in lowering of the pulse rate (increased cardiac efficiency) when another group of muscles, the legs, were put to work. The increased achievement of work by a trained person was attributed to improved vascularization of the voluntary muscles. Although interesting, this thesis, in my opinion, is not conclusively demonstrated.

The method of Stewart for measuring cardiac output has been modified and improved by Wiggers (13) to the end that constantly reproducible measurements of cardiac output have been obtained in a large series of tests on forty-two dogs. The results obtained almost simultaneously by the Fick and the modified Stewart methods were very similar. There appeared to be a definite relation between the constancy of successive measurements and the stability of the blood pressure. In twenty dogs with more stable blood pressures the mean circulatory index (liters of blood per square meter of body surface per second put out by the heart) was 2.77. The peripheral resistance was determined by the formula: Total peripheral resistance (TPR) = (mean blood pressure × 1332) = (cardiac output per second) and expressed in absolute units (A.U.) by making TPR = (dines. sec.)/(cm. 5). The extreme range of values in 145 tests on normal dogs was 3,100 to 9,400 A. U. The methods just described were utilized in a determination by Wiggers & Middleton (14) of the cardiac output and the total peripheral resistance of dogs during the course of standardized hemorrhagic shock produced by hypotension (50 mm. of mercury) for ninety minutes and then hypotension (30 mm. of mercury) for forty-five minutes. A decrease in cardiac output of from 29 to 45 per cent resulted. After reinfusion of the blood the cardiac output again decreased rapidly and low blood pressure resulted. In the final stages the cardiac output became stabilized but the blood pressure continued to decrease. This was attributed to peripheral factors. Changes in total peripheral resistance were extremely variable after hemorrhage and reinfusion.

The effects of renin and angiotonin on cardiac output and total peripheral resistance was studied by Middleton & Wiggers (15) who used quantitative cardiometric methods. Small doses of these

renal preparations produced, in dogs under morphine-barbital anesthesia, slight alterations in cardiac output; larger doses that caused an increase of blood pressure of 30 mm. of mercury or more resulted in a variable reduction in systolic output. The reduction in output was made greater by the decreased cardiac rate produced by the drugs. The cardiac depression may persist for some time following larger doses. On the basis of the cardiac changes observed the authors concluded that the rise in mean arterial pressure following injections of renin and angiotonin gave a fair quantitative index of changes in total peripheral resistance provided small doses were used.

Extensive sympathectomy for essential hypertension gave Gambill, Hines & Adson (16) an excellent opportunity to observe the effect on circulation of certain postures before and after sympathectomy. Among other factors cardiac output was studied by the Grollman method. They found that the cardiac output was greater in both the horizontal and in the 60 degree, head-up posture after splanchnic sympathectomy than before the operation, but was less in the head-up than in the horizontal position both before and after sympathectomy. The operation augmented this difference which was greatest in cases in which marked postoperative orthostatic hypotension developed. There was an increase in stroke volume and in pulse rate after sympathectomy.

By means of electrocardiography and a phonocardiogram Luisada & Mautner (17) carried out a series of interesting experiments in which they studied heart sounds, murmurs, and extra sounds. They were able to produce extra sounds and murmurs by use of drugs and stimulation of vagal nerves. Acetylcholine, epinephrine, nicotine, ouabain, quinidine, and digitalis were among the preparations used. It was concluded that phonocardiography on animals offers a reliable basis for studying functional murmurs and extra cardiac sounds.

From a study of 1,000 cases it was concluded by Friedman & Friedman (18) that the roentgen kymogram is of value as an index of cardiac rhythm and functional capacity and aids in judging the response of the patient to therapeutic measures.

Krañasky (19) from observations in twenty-five cases of mitral stenosis, representative of right ventricular enlargement, twenty-five cases of aortic insufficiency, and twenty-five cases of hypertension representative of left ventricular enlargement found, contrary to the opinion of many authorities, that the apex beat is

shifted downward in right ventricular enlargement whereas in left ventricular enlargement it is shifted outward.

Gibbs (20) has called attention to an important factor in cardiac function that has not been given the place it deserves in the standard works on cardiology. This factor is

> the amazing ability of the heart to handle large, variable streams through markedly angular passages at vastly different pressures and rates varying from zero to high speed without provoking therein measurable eddies.

The disastrous consequences should eddies occur were indicated and an attempt was made to account for their existence in mechanical models and their absence from a properly functioning heart. Although eddies are normally absent, they may appear when the cardiac function or the state of the blood is altered sufficiently as it is in certain anemias.

The influence of measured ergometric (Knipping ergometer) work on the pulse frequency of cardiac patients has been observed by Albers (21) who reported that the type of heart disease did not appear to have an essential influence on the increase in pulse rate resulting from work. There was always an acceleration but it was not proportional to the amount of work. This is not surprising since there would be, even among normal persons, a wide variation in pulse rate in response to a given amount of work.

From observations on patients following pressure on the carotid sinus, injections of acetyl-β-methylcholine chloride (mecholyl chloride) and injections of sympathomimetic drugs Nathanson (22) has made certain deductions concerning the rhythmic property of the human heart. Reflex vagal slowing produced by pressure on the carotid sinus was more marked in the male than in the female and was exaggerated in patients with coronary disease. The rhythmic efficiency of ectopic centers of the human heart is low. Parasympathetic nerves supply mainly rhythmic foci in the atria. Sympathetic stimulation increases the activity predominantly of ventricular foci. Sympathomimetic drugs are the only ones that increase cardiac rhythmicity in states of depression or in the absence of rhythmic functions.

Electrocardiography

In two series of experiments carefully selected as to the initial behavior of the electrocardiogram Bayley, LaDue & York (23, 24) have reported the electrocardiographic changes resulting from temporary occlusion of the anterior descending branch of the left

coronary artery of anesthetized dogs with open chests. By this means they followed the evolution and relief of acute local ventricular ischemia and injury. Three to four seconds after occlusion the positive T wave became inverted and reached its maximal inversion in twenty to twenty-five seconds; by the end of sixty to ninety seconds there were striking RS-T junction displacements. Even though the occlusion was maintained for as long as five minutes, the RS-T junction displacements had disappeared five to seven seconds after the coronary artery was opened and all of the abnormalities in the electrocardiogram caused by the occlusion had disappeared in from five to ten minutes afterward. The authors stressed the point that the changes in the electrocardiogram were like those seen in the development of myocardial infarction in man but, since infarction was not present in the dog's heart, the changes in the electrocardiogram were not owing to the presence of infarction nor did they necessarily indicate its presence. Contrary to general opinion changes of the ischemic type in the T wave constitute the first as well as the last stage in the electrocardiographic evolution of myocardial infarction. Changes in the T wave owing to dissection of the coronary artery or to its occlusion were returned to the control form by injections of theophylline with ethyl diamine which was thought to result from improvement of the collateral circulation. According to the findings of Rosenbaum *et al.* (25) myocardial infarcts produced in dogs by ligation of the anterior descending coronary artery in its middle third do not usually modify the QRS complexes in a characteristic manner in the presence of bundle branch block. The effects of right and left bundle branch block on the electrocardiogram with the use of standard leads have been described. Direct leads from the epicardial surface of an infarct affected the QRS complex by producing an initial R deflection of variable size followed by an S component of similar or greater voltage.

Cats exposed for three days or more to an atmosphere deficient in oxygen showed marked changes in the electrocardiogram (8). There was an increase or a decrease in the height of the T wave in one or more leads, simple inversion of the T wave in one or more leads, depression of the RS-T segment in one or more leads, and cove plane, negative T waves in leads II and III, and a negative T wave in lead I and positive T waves in lead III. Upon returning the animals to atmospheric air all electrocardiographic effects soon disappeared.

From a study of methods of making what they termed "so-called unipolar electrocardiograms" Wolferth & Livezey (26) reported that by pairing an electrode with one placed over the spine of the right scapula one finds less interference with the potential variations of the exploring electrode than in the case of methods that are "unipolar." Helm, Helm & Wolferth (27), after extensive experiments in which the exploring electrode of the electrocardiograph was placed in a wide variety of positions within the gastrointestinal tract and on the body surface, concluded that there is no position below the diaphragm which is superior to the left leg for the study of ventricular electrical activity.

A tilt table in conjunction with an electrocardiograph was used by Bartlett (28) in the study of one hundred patients who had cardiovascular diseases. According to his findings coronary inadequacy was recognized in 91 per cent of the cases. The use of the tilt table was recommended in the differential diagnosis of neurocirculatory asthenia, neurasthenia, myocardial ischemia, and so forth. The results of similar observations on one-hundred persons without cardiovascular disease would seem highly desirable in order that the effect of altered position on the electrocardiogram might be properly assessed.

As a result of rare initiative Kountz & Wright (29) succeeded in obtaining tracings of the total cardiac vibrations from the heart of a convict executed in a lethal gas chamber. The changes in the total cardiac vibrations of the dying human being and of patients with heart disease had similar features and were distinguishable from those of persons without cardiac disease. The possibilities of this technique are intriguing. When sufficiently standardized it may conceivably find important application in cases in which cardiac disease is suspected but not definitely shown by the standard electrocardiogram.

The effects of operation (Beck) in twenty-four cases of cardiac compression and in twenty-one cases of coronary arterial sclerosis were observed electrocardiographically by Feil & Alperin (30). In the former cases a gradual increase in the amplitude of the deflections occurred frequently. The changes in the T wave were inconstant and not uniform in serial records. In the cases in which operation was performed for coronary arterial sclerosis there was a constant pattern of RS-T elevation which gradually disappeared and was succeeded by a sharp depression of the T wave. The greater alterations in the electrocardiogram in the cases of coron-

ary disease were accounted for on the basis of greater injury to the superficial myocardium.

The electrocardiograms of six patients with paroxysmal tachycardia have been analyzed by Decherd, Ruskin & Herrmann (31). The contours of the curves of the momentary electrical axes in these cases resembled those obtained in normal sinus rhythm; only their direction was different. The evidence indicated the presence of an ectopic pacemaker rather than a circus movement in paroxysmal tachycardia.

Rachmilewitz & Braun (32) reported changes in the electrocardiogram in two cases of nicotinic acid deficiency. There were marked changes in the T wave. In one case the T wave was flat in lead I and inverted in leads II, III, and IV before treatment. After six days of treatment with nicotinic acid the electrocardiographic tracing became practically normal in appearance. Withdrawal of doses of the vitamin caused a return of the tracing to the initial appearance but after giving the nicotinic acid again for fourteen days the electrocardiogram became practically normal. Similar results were obtained in both cases so that there appears little doubt that the vitamin deficiency was responsible for the changes observed.

Upper atrioventricular or coronary sinus rhythm produced experimentally by Scherf (33) indicated that stimulus formation in the dog's heart originating in the region of the coronary sinus is accompanied by inverted P waves which are followed by QRS complexes at a normal interval. The author concluded that direct warming of the region of the coronary sinus of the dog's heart through an opening into the right atrium does not cause sinus rhythm but sinus rhythm can be elicited by warming the coronary extension of the atrioventricular node through the wall of the coronary vein.

Darrow & Pathman (34) by recording the electroencephalogram and the electrocardiogram simultaneously on the same graph have shown in human subjects in one-minute periods of overventilation that an increase of heart rate tended to precede or to be simultaneous with the slowing of the electroencephalogram. Many suggestions, among others activation of the vagus nerves, have been offered to account for this finding.

During surgical procedures for relief of vascular disturbances, hypertension, or both, Martin, Miscall & Rovenstine (35) availed themselves of the opportunity of observing the results of direct

stimulation of the celiac ganglion as well as the intact and cut splanchnic nerves. The response to the proper stimulation was a rise in systolic blood pressure, an increase in pulse pressure, transient apnea followed by an increase in respiratory rate with the electrocardiogram showing arrhythmias, and inversion of the T wave. The increase in the heart rate varied from 8 to 22 beats per minute.

Schaefer, Peña & Schölmerich (36) working with monophasic action currents from the apex and base of mammalian (cat) hearts have discussed the effects of their findings on the theory of the T wave. They stated that the form of the normal electrocardiogram with a T wave that has the same direction as the R wave alone cannot be explained by assuming that the stimulation in the heart runs in the shape of a U or any other form of arch. They assumed that the excitation at the base is completed later than at the apex but this is not taken to mean that the base is stimulated for a longer period of time because the course of the wave of stimulation perhaps begins anteriorly, runs over the apex and back to the base. The authors tested, on appropriately arranged nerves, these statements which they had derived from models. It was found that the maximal deflection of the monophasic action current was reached in five to six milliseconds. The conduction time of the stimulus in the fibers of the heart muscle amounted to a little more than one meter per second. The height of the wave of excitation in the mammalian heart was given as 5 mm. just as for nerve and striated muscle.

Athanasiou & Göpfert (37) have reported on the sinus electrocardiogram of cold blooded animals (frog and turtle). The sinus electrocardiogram consists of varying electrical waves mostly of polyphasic form which can be separated from action currents arising from other parts of the heart by slowing the heart by lowering its temperature. Occasionally a diphasic electrocardiographic tracing is obtained from the sinus. The authors were unable to identify with certainty the electrical entity or expression that initiates the heart beat. It was their contention that even if they had, a chemical initiation of the heart beat must be accepted for theoretical reasons. The effect of acetylcholine, epinephrine, and nicotine on the sinus electrocardiogram was described.

Kahn (38) inquired as to whether heart muscle exhibited electrotonus and set about answering the question by using the standard physical methods employed in studying electrotonus of nerves.

She succeeded in demonstrating that heart muscle exhibits electrotonus and that strips of ventricle from the frog behaved in all respects like voluntary muscle.

Effect of drugs.—The rather general use of diphenylhydantoin sodium (dilantin) in the treatment of epilepsy and the toxic symptoms that occasionally follow its use prompted Scherf (39) to observe the action of toxic doses on dogs under pentobarbital sodium anesthesia. Cardiac arrest was caused by 66 to 69 mg. per kilogram. The effects on the electrocardiogram were slow in onset but marked changes appeared in from forty to seventy minutes after injection of the drug. After prolongation of the atrioventricular conduction time the height of the P wave increased with slight widening; then automatic ventricular rhythm appeared. Although the observations were made on only four dogs they were markedly positive and consistent.

Dearing, Barnes & Essex (40) found lesions in the myocardium and alterations in the electrocardiogram following injections of pitressin. There was an increase or a decrease of the height of the T wave, an elevation of the RS-T segment in one or more leads, simple inversion of the T wave in one or more leads, depression of the RS-T segment in one or more leads, cove plane negative T waves in leads I, II and III. Thiamine deficiency is associated with extensive changes in the electrocardiogram in swine according to Wintrobe *et al.* (41). These changes include bradycardia and prolonged PR interval as well as second degree atrioventricular block, abnormalities in the P wave, inversion af the T wave in lead IV, nodal and ventricular premature beats, atrioventricular dissociation, complete block with ectopic ventricular rhythm, and atrial fibrillation. The cardiac symptoms were attributed to the vitamin deficiency and not to inanition. Injections of purified curare (intocostin) did not produce significant changes in the electrocardiogram of human patients with normal or diseased hearts according to Ruskin, Ewalt & Decherd (42). Marked slowing of the heart rate, ectopic beats, and alterations in the P and T waves were produced in the electrocardiograms of dogs and rabbits by Mallach, Marquardt & Werch (43) by injections of toxic doses of trichlorethylene but therapeutic doses of the drug were without effect on the blood pressure and electrocardiogram of normal human patients or patients with cardiac disease. The changes in the electrodiogram of dogs and rabbits were attributed to alteration in the conducting mechanism. An investigation by Heimann & Shapiro

(44) of the effects of N-diethylamino-isopentyl-8-amino-6-methoxyquinoline (plasmoquin) atabrine, and quinine on the electrocardiogram of patients recovering from malaria revealed that plasmoquin increases the size of the T wave above normal and alters the S-T segment so that it simulates that produced by coronary thrombosis. Atabrine decreases the amplitude of the various deflections but affects the T wave most. It can counteract the effect of plasmoquin on the S-T segment. Quinine has an effect on the electrocardiogram similar to but less marked than that of atabrine. Evidence of cardiac effects was not noted in the electrocardiograms fifteen minutes after the intravenous injections of histamine were stopped in a series of twenty-five patients studied by Peters & Horton (45).

Negative electrocardiographic results were obtained by Hafkesbring, Greisheimer & Wertenberger (46) from an extensive series of observations on the effects of sodium sulfapyridine, sulfadiazine, and sulfathiazole.

Action of Drugs

The heart rate of the thyroidectomized rat which is less than normal is restored to normal or increased above normal by proper doses of thyroxin and diiodothyronine, whereas thyronine, diiodotyrosine, and potassium do not have this effect. Dinitrophenol increased the respiratory rate, temperature, and consumption of oxygen but affected the heart rate only slightly. It is suggested by Leblond & Hoff (47) that the effect of thyroxin on the heart rate is not the consequence of general metabolic stimulation but is owing to a direct effect on the heart; thus it may be considered the cardiac stimulant in thyroid preparations. Experiments were done by Gross & Greenberg (48) to determine whether the effect of desiccated thyroid extract alone or epinephrine alone or the two drugs given together was greater on the hearts of thyroidectomized than of intact rabbits. Thyroidectomy appeared to increase the sensitivity of the animals to thyroid extract since cardiac hypertrophy and myocardial damage were more marked in the thyroidectomized than in the intact animals which were given thyroid extract or thyroid extract and epinephrine.

Shaffer (49) produced diuresis in cases of cardiac decompensation by oral but not by intravenous administration of ascorbic acid. In combination with mercurophylline injection (mercupurin) the effect was augmented as much as two and a half times. From ob-

servations on laboratory animals the diuresis resulting from ascorbic acid was believed to result from altered osmotic pressure. Diethylstilbestrol administered daily in 1 mg. doses to oophorectomized rats and male rats for as long as one hundred days did not affect the blood pressure, and heart and respiratory rates (50). The pressor effect of the bitter principle isolated from the seeds of *Securigera securidaca* according to De (51) produces its pressor effect by direct action on the myocardium, the vascular musculature and sympathetic nerve endings. The hypotensive effect of large doses is owing to the stimulation of the vagal center. By means of cross circulation technique afferent impulses responsible for the decreased cardiac rate following injections of veratrone (a veratrum alkaloid) were found by Krayer, Wood & Montes (52) to arise not only in the heart and lungs but also in the region of the carotid sinus. In addition to the reflex effect there was a direct action on the central nervous system causing a vagal stimulation.

Gollwitzer-Meier (53) has investigated the changes in the reaction of the heart produced by epinephrine. In the denervated heart of the heart-lung preparation of dogs epinephrine causes a decrease in pH of the blood in the coronary veins. Initially this decrease is owing to decreased absorption of lactic acid by the heart muscle during a period in which anaerobic energy is used; then in a second phase it is caused by passage of carbonic acid from the heart muscle into the blood. There is a brief decrease in pH after administration of epinephrine but this is succeeded by a long-lasting increase in pH. The author did not investigate the metabolic process that caused this difference but suggested that the alkaline shift of the pH could have a nervous basis. Mendez (54) has studied the effect of simple unsaturated lactones and T-butyl hydrogen peroxide on the isolated heart of the frog. Systolic standstill was produced by certain of the angelica-lactones. This effect is accounted for by the formation of peroxide in the lactone solution. The action of certain lactones on the heart may be prevented by serum globulin, cysteine, glutathione, and diethyldithiocarbamate.

In a study of the acid humoral control of the heart beat Gesell, Mason & Brassfield (55) found that carbon dioxide added to Ringer's solution containing acetylcholine augmented the inhibitory effects of this solution on the action of the heart of the turtle. Immersion of the heart in carbonated Ringer's solution

produced a similar effect. This latter procedure also increased the inhibition produced by faradic stimulation of the vagus nerve. Exposure of the turtle's heart to dilute concentrations of cyanide in Ringer's solution also increased the inhibitory effect of vagal stimulation. Simultaneous exposure of the heart to carbon dioxide and cyanide produced a much greater inhibition than either of these agents used alone. The theoretical implications cannot be recounted herein.

According to the findings of Welsh (56) when insulin is administered to an intact frog, it modifies the reaction of the heart and rectus abdominis muscle to acetylcholine as follows: at 15°C. the responsiveness of the rectus abdominis muscle is increased whereas inhibition of the heart is decreased by acetylcholine; at 25°C. the responsiveness of the rectus abdominis muscle is decreased or subnormal and the inhibition of the heart is increased by the drug. These modifications in response may be owing to changes in the rate of utilization of carbohydrate. Rall, Wells & Dragstedt (57) tested the various digitalis glucosides on the cardio-inhibitory action of acetylcholine in dogs. Lanatosid C invariably abolished the inhibitory effect produced on the heart of anesthetized dogs by appropriate doses of acetylcholine. Lanatosid B was less effective and lanatosid A was much less effective in this regard. A qualitative dissimilarity in cardiac action appeared to exist between the various lanatosides. In line with the last statement but arrived at by entirely different means Moe (58) found a great qualitative difference which was not predictable by assays of lethal doses in the effects produced by the glucosides A, B, and C on the action of isolated hearts of animals. The hearts of dogs and cats were equally sensitive to the cardiac glucosides. The isolated heart of the rabbit required ten times the dosage to obtain the same response as that from the other two species. The relation of the toxic to the therapeutic dosage of the glucosides A, B, and C was not the same although this relation for each of the species was nearly identical. Lanatosid C appeared to offer the greatest margin of safety.

With respect to the influence of acetylcholine on the heart Knowlton (59) has described an interesting and significant series of observations. The action was inhibited for a considerable period by the direct application of intense, single, brief, electrical shocks to the atria of the turtle's heart. This effect could be prevented by use of atropine and prolonged by use of physostigmine which led to the logical conclusion that acetylcholine was liberated by the

vagal nerve endings in a sufficient quantity to produce the observed inhibitory effect.

Fetter, Coombs & Pike (60) investigated the effect of potassium and a cardiac glucoside (strophosid) on the reactions of the heart and stomach of the turtle after stimulation of the vagal nerves. Observations were made on animals after giving potassium chloride, after giving a glucoside, and after giving potassium followed by a glucoside. Sometimes the heart rate was slowed by potassium in the stomach but the heart action was not affected by the glucoside in the stomach. It was concluded that the stomach was, but the heart was not, protected against excess potassium by strophosid. Potassium poisoning was studied from the point of view of the redistribution of electrolytes in the cardiac and skeletal muscles of the cat by Crismon *et al.* (61). Potassium poisoning in cats, as indicated by disappearance of the P wave from the electrocardiogram, occurred when the concentration of potassium reached 11.0 m.eq. per liter or when the rate of rise of potassium exceeded 0.33 m.eq. per liter per minute. Potassium poisoning did not appear to be related to the concentration of potassium in the heart. The uptake of potassium by the heart was associated with the loss of sodium and the appearance of considerable quantities of chloride intercellularly.

The posterior pituitary extract, pitressin, and neosynephrin were employed by Haney *et al.* (62) in an analysis of the role of each vagus nerve in the production of changes in the heart beat of the dog that arise in response to increased blood pressure. Atrioventricular heart block followed the injection of neosynephrin and pitressin in a high percentage of dogs whose right vagi had been cut; this result was in striking contrast to that following injection of the drugs into dogs whose left vagi had been sectioned since atrioventricular heart block did not develop in any of the latter. The difference in cardiac slowing produced by the left as compared with the right vagus was not remarkable. The rate of the completely denervated heart was not inhibited by neosynephrin nor, in the majority of experiments, by pitressin. The effect of another posterior pituitary product, pitocin (oxytocin) on the heart and blood pressure of man has been described by Woodbury *et al.* (63). There is admittedly a considerable species variation in response to this agent but a pronounced effect on the heart and blood pressure of man would not have been anticipated from observations of its negative effect on the circulation of dogs.

It is striking that it decreased the blood pressure of man 30 to 50 mm. of mercury, weakened the cardiac contractions, and usually flattened the T wave which last the authors suggested might be the result of interference by the drug with the oxidative processes of the heart since there was no evidence of decreased coronary flow. Vasodilatation sometimes followed administration of pitocin but this action was thought to be independent and not responsible for the other circulatory changes observed.

Coronary Blood Flow

In confirmation of the results of nearly all of the previous observers using a variety of techniques, Gregg & Shipley (64) using a rotameter for measuring blood flow found that stimulation of the cardiac branches of stellate ganglia produced an increase but never a decrease in the blood flow of the right and left coronary arteries of dogs. These results, with good reason, were interpreted as indicating dilatation of the coronary vessels in response to stimulation of their sympathetic nerve supply. Gregg *et al.* (65) contrary to previously published reports found that increasing the right ventricular pressure by constricting the pulmonary artery caused an augmentation of from 25 to 200 per cent in the blood flow in the right coronary artery and from 19 to 29 per cent in the flow in the left coronary artery. Whether this increase occurs after vagotomy would be of interest to know in view of the fact that increasing the cardiac output (augmented intraventricular pressure) increases the coronary flow in the innervated but not in the denervated heart.

Pathological Physiology

Sudden death of an apparently healthy athlete was accounted for by Raab (66) on the basis of an excessively high concentration of epinephrine-like substances in the cardiac muscle which, judging from data obtained from the hearts of animals and man, was too great to be compatible with life. As the author pointed out, chemical examination of the heart muscle may have medicolegal value in cases of unexplained sudden death particularly when death has occurred under emotional or physical strain. It would be interesting to know the blood potassium level in such cases as Raab has described in view of the report by Keith, Burchell & Baggenstoss (67) in which death of three patients with severe renal insufficiency was accounted for on the basis of potassium intoxication.

Electrocardiographic abnormalities suggestive of myocardial

infarction or coronary thrombosis were seen by Gottesman, Casten & Beller (68) in cases of acute pancreatitis in man and were reproduced in dogs with acute pancreatitis. Recovery from the abdominal irritation was accompanied by return of the electrocardiogram to normal appearance.

Ungerleider & Gubner (69) analyzed 1,142 cases in which extrasystoles were present. Evidence of heart disease was found in only 42 per cent. Symptoms of palpitation do not have great significance since they occur both in normal subjects and in those with heart disease.

Starr (70) has made an important application of the ballistocardiograph to military medicine. By its use objective evidence of abnormality was obtainable in most persons whose condition had been designated as neurocirculatory asthenia. Malingerers can be detected with considerable ease and this method should find use in indicating whether a man is physically fit for military service.

Marked cardiac hypertrophy and nephrosclerosis was reported by Selye & Hall (71) in male white rats that had received proper amounts of desoxycorticosterone acetate along with overdosage of sodium chloride. Darrow (72) observed necrosis of the myocardium and cellular infiltration resulting from injections of desoxycorticosterone acetate into rats kept on a diet low in potassium. After only four days a loss of potassium and a gain in sodium occurred in the heart.

Signs of severe myocardial damage have been seen by Houchin & Smith (73) in rabbits deprived of vitamin E. They could be killed by much smaller doses of posterior pituitary extracts than were well tolerated by normal controls but they were highly resistant to the toxic effects of the cardiac glucosides. Cardiac dilatation occurred and death was owing to myocardial failure.

Cardiac enlargement mainly owing to dilatation of the right atrium was seen in rats kept on a thiamine deficient diet by Ashburn & Lowry (74). The atria of most animals showed necrotic lesions of the muscle fibers (6, 20). Similar lesions were seen in the ventricle of only a few animals. Inconstant conditions such as fluid in the abdominal or pleural cavity and atrial mural thrombi were seen in a few animals. Inanition was ruled out as a factor in the development of the cardiac lesions (32). Fox & Jones (75) found mild vascular and perivascular changes limited almost exclusively to the smaller branches in the hearts of white rabbits after parenteral injection of horse serum. All rabbits that showed a necrotic

type of skin reaction when horse serum was injected had vascular lesions. Hueper & Ichniowski (76) as a result of histamine shock in dogs observed late vascular and cardiac lesions as well as lesions of certain other organs after acute but prolonged hypotension (30 to 40 mm. of mercury) in dogs. The lesions consisted of degenerative cystic and calcifying regions in the aorta and smaller vessels, such as the carotid, coronary, cerebral, and gastric arteries. Could the changes observed have been owing in part to the long period (one and two hours) of hypotension? The animals were given also methyl cellulose in saline solution to which S-methyl isothiourea had been added. It is not stated whether the latter had any effect.

Spontaneous interstitial myocarditis has been observed by Torres (77) in apparently healthy adult dogs and to a less extent in pups. The condition apparently was not due to infestation by the common parasites that might have been suspected.

Endocarditis lenta has been successfully produced in rabbits by MacNeal, Spence & Slavkin (78, 79) by repeated intravenous injections of *Streptococcus viridans* of proper virulence. The bacteria were phagocytosed and in some places, particularly on the heart valves, the included bacteria proceeded to develop the vegetations of endocarditis. The lesions closely resembled those seen in man. Using the same organism, Loewe, Rosenblatt & Lederer (80) produced subacute endocarditis by similar means in 50 to 100 per cent of their rabbits. They continued their injections until positive blood cultures, loss of weight, and the development of cardiac murmurs indicated the presence of endocardial vegetations.

In a series of thought-provoking papers Starr, Jeffers & Meade (81) have presented experimental data which have led them to doubt the teaching that failure of the right side of the heart is the predominant factor in peripheral venous congestion in man. The right ventricular walls of dogs' hearts were seriously injured but only a minimal increase in peripheral venous pressure occurred. These authors suggested that there are factors concerned with blood volume and the tone of the blood vessels which are more likely than failure of the right side of the heart to be able to produce peripheral venous congestion. Kalter & Grishman (82) in a study of the relation of pulsus alternans to electrical alternans concluded that the underlying mechanism is the same in both, namely, a disturbance of the nutrition and metabolism of the myocardium.

In an experimental study for which the white rat was used

Hellwig (83) investigated whether anatomic changes can be demonstrated in the hearts of animals with simple goiter. It was concluded that there is no anatomic type of simple goiter that predisposes to cardiac complications. Among other results they found that a systolic murmur often is present in marked tachycardia and is independent of pressure conditions.

Methods

A new cardioscope has been developed by Harken & Glidden (84) and it has been used successfully in visualizing intracardiac structures. This is made possible by a transparent balloon covering the end of the scope. The balloon is distended with saline solution and as it comes into contact with the walls of the heart, the blood is displaced and the structures are rendered visible.

An electrical unit has been developed by Shipley & Crittenden (85) for use with the rotameter. Recordings of blood flow with an error of 5 per cent or less are possible. Since special training or technical knowledge is not required for its use and since continuous recordings of blood flow are possible without any attention from the operator, this method should find a place in every laboratory of physiology.

Rappaport & Rappaport (86) have presented experimental evidence that the average commercial electrocardiograph (both the Einthoven string and amplifier types) are incapable of registering the cardiac action potentials of small animals with any degree of accuracy. A method for the accurate recording of electrocardiographic complexes of animals with heart rates of 750 beats per minute has been described. It consists of employing an electronic booster or amplifier in conjunction with a high natural period galvanometer. Two types of electronic amplifier may be used for electrocardiography; namely, the resistance capacity coupled and the direct coupled. The former is preferred. For an adequate concept of the apparatus and the interesting theoretical treatment of the subject the original article must be consulted.

A direct current amplifier for recording changes in capacitance has been described and certain theoretical considerations of capacitance have been discussed. The results obtained with the amplifier have only qualitative and empirical significance (87).

A new form of myocardiograph has been designed by Jackson (88) that reduces to a minimum the effects of the movements of the lungs on the tracing made by the heart.

Foulger & Smith (89) have described a differential heart sound meter; this apparatus for measuring the distribution of energy in heart sounds can be used to study physiological changes in man as well as in dogs and small experimental animals. Particular attention has been given to changes resulting from exposure to toxic chemicals.

A ballistocardiograph has been combined with a tilting table by Wilkins (90) to permit the taking of records in any position. Records in the steeply tilted positions have been complicated by the muscular tremors of the subject.

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ELECTRICAL ACTIVITY OF THE BRAIN

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The present review is the third dealing with the electrical activity of the brain to appear in this journal; the first was by Davis (1) in 1939 and the second by Jasper (2) in 1941. References included in previous reviews will not be specifically mentioned in this one which deals only with articles published between the first half of 1940 and 1944. No attempt is made to credit work to the original investigator. The purpose of the present review is to bring the reader up-to-date, to add pertinent information, and suggest concepts that may help in understanding the phenomenon under consideration. For sins both of omission and commission apologies are made in advance. The former are undoubtedly the more numerous, for it is impossible to mention all observations.

The general subject of bioelectric potentials has been reviewed by Bishop (3) and Gerard (4) and the electrical activity of nervous tissue by Grundfest (5). Physiological neuronography and functional organization of the brain will be touched on only briefly because they have already been recently considered by McCulloch (6). Two monographs on electroencephalography (7, 8) and several reviews of the subject (9 to 13) have appeared since the publication of Jasper's article. A large number of articles have appeared on clinical aspects of electroencephalography; only those that have important physiological implications will be mentioned here. Reviews of the clinical literature can be found elsewhere (7 to 11, 13). It has been impossible to obtain a complete bibliography of articles published since the beginning of the war in enemy countries and in enemy-occupied territories.

The war has interrupted much important investigation, but it has stimulated certain lines of research, particularly in regard to the use of electroencephalography as a screening technique to prevent epileptics from entering military service (14, 15, 16). The hope that it would be useful for selecting a superior group for flying training (17) was not fulfilled (18). It has been extensively applied to the study of brain function under low oxygen pressures (19, 20, 21) and in the investigation of "blackout" such as is ex-

perienced during dive bombing (22). In the hope of improving the treatment of the wounded, it has been used for the study of head injuries (23 to 29). Large amounts of control data have been collected on men of military age (14, 17, 18, 30).

Much of this war-inspired research was carried out with the aid of government funds and its publication restricted or delayed. However, almost everything of importance has now either been published in full or released in the form of brief abstracts. Therefore, the publication of secret military papers after the war is not likely to reveal anything startlingly new.

General Characteristics

In general, an inverse relation is observed between the amplitude and the frequency of this electrical activity, but there appear to be certain resonant frequencies such that when the oscillations attain one of these (for example, 10 per sec.) amplitude increases (31, 32). From this it follows that stimulation may produce either a decrease in amplitude or an increase depending upon the "frequency setting" prior to stimulation and the frequency developed as a result of stimulation (31, 32, 33). It is hazardous to describe a change by saying that activity is increased or facilitated and better to describe the change in terms of alterations in amplitude and in frequency. The most usual response to afferent stimulation on the unanesthetized animal is an increase in frequency and a decrease in amplitude of the spontaneous activity.

It is at times profitable to regard the brain as a population of interacting neural elements possessing certain properties in common but also separated into groups or classes having somewhat different characteristics (31 to 34). One of these specific characteristics is a tendency to show activity at a particular frequency, for although all frequencies between 0 and 100 or even higher can be recorded from the brain, the amount of activity (voltage) recorded in certain frequency bands is higher than in others. This assumes that the rhythm of the elements that beat at a given frequency is somehow synchronized, otherwise the phase relations would be entirely random and no voltage would be recorded at that frequency.

Steady high voltage activity tends to spread to areas showing less steady or lower voltage activity. Specific pathways are of importance in determining spread, and differences in cortical struc-

ture must also be taken into account, but in the cortex, pacemaker activity seems to be fairly diffuse; it varies from individual to individual and changes with circumstances in the same individual.

Basic Physiology

The basic physiology of the electrical activity of the brain is still not understood. Little information is available on the following important topics: (*a*) the part of the neurone from which the potentials arise, (*b*) the type of interneuronal coupling that results in the development of the fairly large voltages commonly recorded, (*c*) the nature of the potentials (are they polarization-depolarization potentials associated with varying metabolic rate in nerve cells or summated action potentials of a more or less familiar type?), and (*d*) the chemical reactions giving rise to them. However, all these problems are under investigation and, as will be indicated in the body of this review, progress is being made toward their solution. Electrical waves recorded from the brain may, under various experimental conditions, despite a superficial resemblance, have various origins and show highly contrasting types of behavior. Differences between species are important (35). The structural integrity of the brain, the presence or absence of anesthetic, the type and amount of anesthetic, the nutritional state of the brain, and age are all determining factors.[1]

Spontaneous Activity in Unanesthetized Animals

Experimental lesions.—The question as to what parts of the brain generate spontaneous electrical activity in the normal waking animal has been investigated by lesion experiments. In the monkey, removal of large sections of the cortex does not interfere with the waking spontaneous activity of what remains (36) but enucleation of the thalamus on one side reduces the spontaneous activity

[1] It is incumbent on the investigator to answer either directly or by implication the following questions when reporting observations: What species was used? What was the age of the animals? How were they selected from the general sample? Was an anesthetic employed and if so which one and how much? Was respiration spontaneous or artificial? What was the general level of blood pressure? From what area or areas was the record taken and what was the orientation of the electrodes? Was the structure of the nervous system damaged? What type of stimulation was applied and where? With the answers to these questions many apparent discrepancies between the observations of different investigators can be resolved.

of the ipsilateral cortex to low voltage slow waves (37). Lesions of the caudate nucleus result in the appearance of high voltage slow waves over the ipsilateral cortex (37, 38).

Clinical lesions.—In man there are no lesion studies that exactly correspond to those carried out on animals. However, extensive cortical atrophy (39) and subcortical destructive lesions (40) in human cases, like cortical ablations in animals, can occur without electroencephalographic abnormality, and bifrontal lobotomy does not perceptibly modify the electroencephalogram (41). No reports have appeared of destructive lesions in the depths of the brain producing changes comparable to those seen by Kennard & Nims in monkeys (37, 38). It is true that lesions in the region of the third ventricle and the anterior end of the aqueduct produce pathological sleep accompanied by activity that is in one sense abnormal (42), but it is indistinguishable from that occurring in normal sleep. In Sydenham's chorea, the major lesion is supposed to be in the basal ganglia, and high voltage slow activity is common (43, 44). This has been cited by Kennard as an example of abnormality associated with a basal gangliar lesion. However, in the acute stage when electroencephalographic abnormality is most common (7), there is good clinical and pathological evidence that the pathological process invades the cortex (45). To stress the importance of basal-gangliar pathology in the production of electroencephalographic abnormality in this condition seems unwarranted for no less and no different abnormality occurs in cases of cortical encephalitis without evidence of a basal-gangliar lesion (46). Moreover, Wilson's disease, Parkinsonism, and Huntington's chorea, all associated with basal-gangliar lesions, do not necessarily show electroencephalographic abnormality (47).

The preponderant clinical evidence indicates that a purely destructive lesion, no matter where located, is less effective in producing electroencephalographic abnormality than an inflammatory or irritative one. Most cerebral lesions in man are due to failure of blood supply, hemorrhage, infection, or dislocation, and these are commonly associated with extreme electroencephalographic abnormality. When located in the cortex, they are more effective in producing electroencephalographic abnormality than when subcortical. The amount of tissue involved and the rapidity with which the process has developed are, however, important determinants. It can therefore be concluded that the electroen-

cephalogram is a delicate indicator of cortical injury and of certain types of dysfunction related to epilepsy: it is an insensitive indicator of loss of brain substance.

Localized abnormality.—Localized cortical damage so commonly causes localized abnormal activity that electroencephalography has become a standard clinical procedure for detecting lesions in the accessible cortex (48). Some abnormal wave forms are particularly likely to be focal (49, 50), and certain wave forms are more suggestive of gross pathology while others tend to occur without demonstrable lesions (49, 50).

Amplitude asymmetries.—Differences in amplitude in homologous parts of the two hemispheres, without abnormality of frequency or wave form, occur in a variety of conditions such as subdural hematoma, bleeding from cerebral aneurisms, concussion, and lesions of the visual system. Case (51) and Woodhall & Lowenbach (52) report that the maximal damage is on the side of lower amplitude. However, although this relationship is usual, there are so many exceptions that amplitude-asymmetry cannot be used as a reliable lateralizing sign (53, 54). A certain degree of amplitude-difference is commonly encountered in normal persons, and alpha (8 to 12 per sec.) activity is usually higher on the right than the left (32, 55). Fine discrimination between minor differences in the amount or voltage of alpha activity in the two hemispheres is without value for clinical localizing purposes (55). Douglass has found, however, that stutterers tend during silence to have more unilateral blocking of alpha activity on the left whereas normals tend to have more on the right (56). This observation has been confirmed by Knott (57).

Sensation and movement.—Frontal, central, occipital, and temporal areas tend to show somewhat different activity, but pronounced differences corresponding to architectonic differences, as previously described by Kornmueller in rabbits, are not generally observable. Von Ledebur (58), working on rabbits, agrees that such differences are present, but states that they are abolished by fright and by light dial anesthesia. Kornmueller (59) has studied the effects in man of voluntary movements of the limbs and of various types of stimulation. He reports that moving an arm or leg causes a diminution in amplitude which is maximal over the central areas. Touch and auditory stimuli cause a similar response in the central areas. Visual stimuli, however, produce a maximal

change in the occipital areas. No reference is made to unilateral effects and it can be assumed that these were not observed. Toman (34) was unable to produce unilateral effects by illuminating part of the retina.

With a flickering light, a rhythm can be established in the occipital area that will follow the flicker frequency (34, 60, 61, 62). In some subjects, rhythms from 0 to 24 per second could be produced (34). A response of double the flicker frequency was at times obtained. The average lower limit of frequency that the cortex followed was 6.5 per sec. The average upper limit was 16.5 per sec. Flicker-following is best seen in persons with weak alpha rhythm, i.e., a strong alpha rhythm interferes. As the flicker-stimulus approaches 10 per second, the amplitude of alpha activity (34, 60) and the sensation of brightness reach a maximum (34). A full discussion of this subject with complete references to the literature will be found in the report by Walker and collaborators (62). The time required for the reappearance of alpha potentials after photic stimulation has been shown by Motokawa & Mita (63) to vary directly with the brightness of the light. These authors found repeated touch less effective than photic stimulation in blocking alpha activity and mental arithmetic less effective than touch. A moving shadow was highly effective and it greatly delayed adaptation to photic stimuli. A combination of touch and mental arithmetic with visual stimulation was less effective than visual stimulation alone. During after-images, according to Motokawa (64), alpha activity was depressed and replaced by 6 per sec. waves. In the dark period between after-images, alpha wave spindles appeared. Stimulation of any type, except visual, during the blocking associated with after-images, resulted in the appearance of alpha activity. Latency in blocking of alpha potentials with light was unaffected by the strength of the stimulus (65).

Observations on hysteria (66) and hypnosis (67) indicate that blocking of the alpha activity occurs even though the subject reports no sensation; thus the EEG under properly controlled conditions can be used to distinguish between organic and functional sensory defects.

The conditioning of the alpha rhythm in man has been studied by Jasper, Shagass, Knott, Henry, and Johnson (68 to 72).

The individual differences encountered in waking human electroencephalograms (73) disappear in sleep (74), but, just before

sleep, subjects who show little alpha activity in the waking record show bursts of such activity. The Fourier transform of the electroencephalogram indicates that during sleep all components of the electrical activity of the cortex are slowed (75).

Spontaneous Activity in Anesthetized Animals

Numerous investigators have studied the spontaneous activity of the pentobarbitalized cat's brain. Afferent stimulation increases the frequency of this activity (76). The burst of 5 to 10 per sec. waves occurring with moderate depths of anesthesia are not altered by removal of the contralateral cortex (76, 77) or extensive lesions in the ipsilateral cortex or by ablation of the cerebellum (76). Such bursts disappear, however, if the ipsilateral thalamus is enucleated (76, 78, 79). This 5 to 10 per sec. burst activity is mediated by a system of diffuse cortical afferents from the medial nucleus of the thalamus (79, 80).

A second type of spontaneous activity in the anesthetized cat is referred to by Dempsey & Morison (80) as "projection-activity." It has a frequency faster than 12 per sec. and, unlike the bursts of 5 to 10 per sec. activity, it is not generalized but is confined to the specific projection areas for cutaneous sensation. It is further differentiated from the 5 to 10 per sec. burst by the fact that it is decreased by decerebration. A third type of spontaneous activity consisting of slow waves has been dsecribed by Dempsey & Morison, but since it appears to be identical with an induced unsustained response, it is considered in detail in the following section.

In chronic preparations, reduction of the motor cortex of the monkey to its inner two layers greatly reduces the amplitude of spontaneous activity recorded from the injured area under dial anesthesia (81).

Induced Unsustained Activity

General characteristics.—If a single shock is delivered to an afferent system or association pathway, a spike is obtained from various fiber tracts, relay nuclei, and from the terminal cortex. Such spikes are best seen and most precisely localized if spontaneous activity and spread are decreased with an anesthetic. Curtis (82, 83), working on cats under barbiturate anesthesia, found that an oncoming impulse produces a negative wave if the stigmatic electrode is in an activated fiber system, and a positive wave if it is

just outside and beyond an activated fiber system. With one electrode on the sensory cortex, an afferent volley fired into it produces first a positive wave for the reason stated above, i.e., the active electrode is outside and beyond the activated fiber system. This positive wave, which commonly appears as a spike, is followed by a negative wave (or a series of negative waves), the result of the firing of cortical elements. The negative or purely cortical wave is depressed by local application of pentobarbital and enhanced by local application of certain convulsants, whereas the positive or incoming fiber discharge is not greatly altered (83, 84). The differential effects of various drugs on the primary spike and on the secondary waves have been considered in detail by Bremer (85). He reports that in the auditory cortex of the unanesthetized cat with a low brain stem section, strychnine increases the amplitude of the primary spike and does not alter (or in large doses actually depresses) the secondary waves. Acetylcholine and substances with a nicotine-like central action increase the secondary waves without increasing the primary spike. Barbiturates, in hypnotic doses and also natural sleep, depress electively the secondary waves, while ether has an equal effect on both the primary spike and the secondary waves. In large doses, barbiturates greatly depress or abolish the secondary waves and increase the amplitude of the primary spike. When records are made from the primary projection-areas for either touch (86), hearing (85, 87, 88) or vision (89), a brief afferent volley produces a positive spike, but when recorded from the pyriform lobe (90), i.e., olfactory cortex, the spike is negative. This, according to Fox and his collaborators (90), is not an exception to the rule stated by Curtis, but is in agreement because the afferent fibers to the pyriform lobe run tangentially over its surface.

In pentobarbitalized cats, using photic stimulation, Walker and his co-workers were able to drive the optic nerve, geniculate, and cortex at 62, 59 and 34 cycles per sec. respectively (89). They conclude that fusion in the cortex limits temporal resolving power of vision. In the unanesthetized cat with a low brain stem section, Bremer (85) was unable to obtain from the cortex frequencies above 70 per sec. in response to auditory stimulation.

Specific afferent systems.—With the aid of induced unsustained spike potentials produced either by sensory or electrical stimulation, it has been possible to determine with precision the fiber

systems, nuclear relays, and cortical projection areas for touch (86, 92), vision (2), hearing (85, 88, 91, 93), and smell (90, 94). Peripheral and central afferents to the cerebellum have been studied by Dow (95, 96). The limits of this review do not permit a discussion of these important anatomical relations. The response to tones in the auditory cortex of the unanesthetized cat with a low brain stem section is determined by the strength, frequency, and duration of the stimulus. As will be noted below, Rosenblueth & Cannon have shown that the induced, self-sustained response is determined in like manner. No evidence could be found by Bremer for tonal localization in the cortex. However, when the response to a single tone became "fatigued," the original amplitude of the response could be restored by changing the tone slightly. This, Bremer believes, suggests that different chains of sensory neurones are specialized for the reception of different tones.

Diffusely radiating afferent systems.—The unsustained response of the pentobarbitalized cat's brain to stimulation has been studied intensively by Dempsey & Morison (97 to 104). In addition to the spikes referred to in the preceding section, which are discretely localized in the cortex and are identified with the long fiber pathways mediating special sense, these authors have distinguished two other fundamentally different types of response mediated by diffusely radiating afferent systems (98, 100, 101): (*a*) medium frequency potentials (5 to 10 per sec.)—these are recorded from the entire cortex, but can be evoked or augmented by stimulating certain localized subcortical structures, especially the medial nuclei of the thalamus and they are closely related to or identical with the spontaneous burst potentials, (vide supra): (*b*) slow waves (2 to 3 per sec.)—these also are recorded from the entire cortex and are identified with structures lying in the rostral part of the amygdaloid nucleus, the anterior commissure, and possibly the fornix. Both these systems are apparently capable of producing spontaneous activity. The discovery of these two diffusely radiating nonspecific afferent systems is of major importance. They are referred to as nonspecific because they do not mediate any special sense. Nevertheless, they probably subserve some specific function. What that function is remains to be determined, but diffuse afferent systems have been hypothecated to account for the generalized cortical changes seen in sleep, attention, and seizures.

Evoked sustained potentials.—If the activity of an area is greatly

augmented by the use of strychnine or other convulsants or if the area is strongly stimulated, a special type of activity appears which is characterized in general by its relatively high voltage, but more especially by the special patterns and wave forms that appear.

McCulloch and his collaborators have continued the work begun with Dusser de Barrenne in which the strychnine spike is used not only to chart the course of cerebral pathways, but also to determine the function (6), sensory (105), motor (106), excitor or suppressor (107), cortical (108, 109), and subcortical structures (110 to 115). It has been found that the suppressor areas in the cortex send projection fibers to the caudate nucleus (113). Here the somatotopic arrangement clearly evident in the thalamus and cortex is lost, but a corticotopic arrangement takes its place, i.e., what was anterior in the cortex is anterior in the caudate and what was posterior in the cortex is posterior in the caudate (115). The changes that occur at the site of strychninization are considered in detail by McCulloch (115). He has shown that the spike is recorded as negative if the active electrode is in the region where the spike occurs and positive a millimeter away. In this and other respects, it resembles the preliminary spike of the induced unsustained response and McCulloch believes that it follows "normal pathways." The best assurance that these pathways are real, rather than "pharmacological artifacts," derives from the high degree of correlation found between the data obtained with this method and anatomical connections as determined by other methods.

Disturbances evoked by strong electric stimulation have been studied by Rosenblueth & Cannon (116). To these they apply the term self-sustained responses. They can be properly regarded as after-discharges. This corresponds closely to what Kornmueller called *Krampfstroeme*, and others have called seizure-discharge or seizure-waves. The specific discharges described by Rosenblueth & Cannon most closely resemble seizure discharges of the tonic-clonic type and the authors refer to them as a tonic-clonic response. Chloralose, the anesthesia employed in most of their work, favors spread and makes the cortex respond as a unit, whereas dial opposes spread and allows a considerable degree of independence to different cortical areas. In monkeys under chloralose, localized stimulation in various cortical areas resulted in self-sustained responses, but these were never obtained from the caudate nucleus, the basal ganglia, or cerebellum. (Clinical convulsions are com-

monly associated with cortical lesions, but rarely with subcortical or cerebellar lesions.) Whether a sustained response is obtained, its amplitude and degree of spread are determined by the voltage, duration, and frequency of the stimulus. With both electrodes on the brain, the voltage of the response varies with the distance between electrodes, this fact indicating asymmetric charges on parallel elements. The sign varied with electrode depth and also with the cortical area. No fixed relation could be made out between direction of spread and the sign of the disturbance. Both indiscriminate and preferential spread occurred. The pace-maker area for clonic activity is not necessarily the stimulated area, for, as with Jacksonian seizures, once the discharge has begun to spread, the starting point can be ablated, yet the disturbance continues. Under chloralose anesthesia, the clonic phase of the self-sustained response tends to cease in all cortical areas at once. This, Rosenblueth and his collaborators believe, occurs because the frequency of the clonic discharge drops to below one to one and a half per second, a rate at which stimulation is relatively ineffective (116) and "background-excitation" becomes insufficient (117). The observation (116), that narrowing the gap between the recording and the stimulating electrode to only one or two millimeters does not modify the appearance of the slow waves, indicates that they are not the result of summated fast waves similar to axone spikes as hypothecated by Adrian. McCulloch's suggestion that activity of the type under consideration is due to reverberating neurone circuits is rejected by Rosenblueth & Cannon (116) on the following grounds: (*a*) the frequency of the discharge should be related to the length of the circuit and the characteristic changes in frequency that occur in the course of a self-sustained response must be explained by elaborate sub-assumptions: (*b*) the duration of the response should depend on the characteristics of the reverberating chain; it does not, but depends rather on the "quantity" of stimulation; (*c*) the simultaneous cessation of clonic activity all over the cortex is difficult to explain in terms of reverberating chains; (*d*) isolation of a region by section does not alter the clonic rate; (*e*) the cerebellum also has neurone circuits, but does not show this type of self-sustained activity.

Libet & Gerard (118) have shown that the high voltage spikes produced in frogs by caffeine are modifiable both as regards their sign and their locus by polarizing voltages.

No attempt has been made to drive spontaneous clonic activity

in man, but it has been shown that strong visual and auditory stimulation, particularly the latter, can in some cases cut short a petit mal seizure (119) and attention has a similar effect (120). Induced self-sustained activity in man is followed by a period during which a previously adequate stimulant can no longer produce a sustained response, i.e., a second seizure (121). This period of depression may be followed by a brief period of hyperexcitability in which the threshold for a sustained response is lower than before the convulsion.

The production of self-sustained responses (convulsive seizures) in man by electric stimulation of the brain (122, 123, 124) or with drugs (125, 126, 127) is now a commonplace clinical procedure. Its therapeutic efficacy in depression and in some types of schizophreniform psychoses is generally admitted and a vast amount of observation and experimentation is being carried on in this field. All who have studied therapeutic convulsions agree that they are commonly followed for an hour or more by an increase in slow activity. Repeated convulsions still further increase the amount of slow activity and delay its disappearance. In some cases permanent slowing occurs. The changes are maximal under the stimulating electrodes (128).

By simultaneously recording pH and the electrical activity of the cortex during metrazol convulsions, Jasper & Erickson (129) determined that the excessive neuronal activity of the convulsive discharge is associated with an acid shift in pH, but this is secondary to the discharge. The normal vasodilator response to acid metabolites tends to present such a shift but is usually overwhelmed. No evidence could be found of a consistent or significant alkaline shift before the seizure discharge.

By the ampermetric recording of oxygen tension prior to and during a seizure discharge, Davis, McCulloch & Roseman (130) have determined that during all ordinary types of seizures, the oxygen tension of the cortex falls to asphyxial levels. This drop in oxygen tension starts even before the appearance of seizure waves. With methylguanidine which induces aerobic glycolysis, seizure discharges appear that do not run the typical course (131); a high voltage fast discharge develops which goes on and on without a change in frequency and does not subside until the death of the animal. This seizure is associated with a rise in oxygen tension. These observations indicate that in the usual type of seizure, even

before the appearance of the discharge, a chemical process has developed that consumes an excessive amount of oxygen, and that during the convulsion, in spite of the great increase in blood flow, the oxygen consumption is so great that near asphyxia develops. However, the studies with methylguanidine show that high voltage discharges, with most of the characteristics of seizure discharges, can appear in the absence of a decrease in oxygen tension, and actually do appear in the presence of an increase.

Del Pozo & Leão (132) report that acapnia and anemia independently diminish the tonic-clonic response to cortical stimulation. Libet and his co-workers (133) report that with metrazol and strychnine slower but otherwise typical self-sustained responses can be obtained from the relatively inactive cortex of young kittens.

Clinical Correlations

Epilepsy.—Epilepsy is characterized by paroxysmal discharges essentially like those described as self-sustained responses (134 to 137). Failure to recognize that distinctive types of discharge are associated with different types of clinical seizure (135) results from failure to make the required clinical and electroencephalographic distinctions (136). All factors that are important in determining the behavior of cortical potentials are also important in epilepsy. The hereditary factor has been further confirmed by studies on identical twins (138).

Post-traumatic state.—Severe head injuries are commonly associated with convulsions, but even when these do not occur the electrical activity of the cortex is likely to become abnormal. References to the clinical literature are given in the first section of this review. Mild head injuries do not show significant abnormality (27), but the response to overventilation may be increased (28).

Williams & Denny-Brown (139) found that concussion is accompanied by flattening of activity which is followed, after a variable interval, by continuous slow activity. This later becomes discontinuous (23, 24, 139), i.e., the slow activity appears in bursts. These bursts become fewer and shorter with advancing time and the frequency of the slow waves in the bursts becomes higher until normal frequencies are attained (23, 24, 29). Failure to show improvement or the intercurrent appearance of seizure discharges are ominous signs suggesting that post-traumatic epilepsy is im-

pending (23, 24, 29). Walker reports an important phenomenon that is omitted from this description (140). Immediately after the blow a very high voltage, very rapid discharge occurs. Thus, concussion can be regarded as a violent seizure or a maximal discharge that is compressed into a fraction of a second, leaving the brain in a state of electrical inactivity comparable to that occurring in post-epileptic stupor. This maximal discharge is apparently the result of the simultaneous mechanical stimulation of a large number of neural elements.

Other disorders.—No important correlations have yet been found between the major psychoses (manic-depressive and schizophrenic) and the electrical activity of the cortex (141 to 144). Numerous workers have pointed out that the important correlation that has been demonstrated is with epilepsy and "organic" brain disease (145, 146, 147). Not all organic brain disease, however, shows electroencephalographic abnormality (39, 40); it occurs chiefly in association with irritative lesions and metabolic or epileptic type of disorders.

Slowing of the EEG during pregnancy with a rebound to normal or faster than normal frequencies after parturition has been reported (148). It might be expected that pregnancy would be a period during which defective control of cerebral activity as it occurs in epileptics would tend to manifest itself. This is in line with the observation of Rosenbaum & Maltby (149) that epileptic types of abnormality are found in patients with eclampsia, and an excess of electroencephalographic abnormality in their near relatives. General clinical experience, however, indicates that pregnancy in epileptics does not tend to be associated with an exacerbation of their disorder. It seemed reasonable to suppose that the changes noted in normal women with the menstrual cycle (150) might be due to changes in estrogen or progesterone, but Cress & Greenblatt (151) found no effect of these substances on the electroencephalogram.

The changes that occur in Addison's disease and hyperinsulinism are referred to in the section on sugar and those occurring in parathyroid disease are considered under disturbances in electrolyte balance. Studies on hysteria and malingering are considered in the section on spontaneous activity.

Various workers have reported an excess of electroencephalographic abnormality among persons with behavior disorders of psy-

chopathic personality (152 to 163), but when corrections were made for age (164) and when special types of behavior, namely epileptic and post-encephalitic, are eliminated (164, 165), the incidence of electroencephalographic abnormality falls to the level encountered in the control group. The significant association resides, therefore, in the groups with epileptic or post-encephalitic types of behavior (165).

General Factors

Age.—The importance of age as a determinant of cortical activity in the early period of life has been reemphasized by the studies of Kennard & Nims (166) on the infant macaque, and of Libet and his collaborators (133) on the cat. Their findings are in general accord with those reported on man, the chief difference being related to the more rapid rate of maturation of the monkey and the cat. Kennard & Nims (38) also mention the fact that young animals show more electroencephalographic abnormality after a given lesion than old animals; this is in accord with clinical experience. The electroencephalogram of the fetus *in utero* has been recorded by Lindsley (167). It seems reasonable to suppose that the fetus was asleep, for only in sleep does the newborn human infant show anything that can be reliably interpreted as electrical activity of cerebral origin.

Robinson (168) reports that young epileptics are more likely to show slow high voltage activity with overventilation than old epileptics. Brill & Seidemann (169) confirm the opinion that this is also true of normal children and the same observation has been made on psychotic patients by Liberson & Strauss (170). A study showing the incidence of various degrees of response to overventilation at different age levels has been reported by Gibbs, Gibbs & Lennox (171). The results were in line with previous studies, but because the data include a large number of cases in each age group and, since the age range is considered from early childhood to old age, they afford a basis for estimating the normality of a given response to overventilation at a given age.

That the influence of age on the resting EEG continues into adult life was shown by Knott & Gibbs (172) from data obtained with the Grass frequency analyzer. Accumulation of more data shows that these changes are sufficiently gross to be evident from inspection of the unanalyzed EEG (164). They are roughly

summarized by the statement that the electrical activity of the cortex becomes faster with increasing age up to the age of sixty. These findings and those on psychotic patients by Greenblatt (173) require that age be carefully controlled in all electroencephalographic studies, and that norms be established for different age ranges.

Autonomic nervous system.—A curious phenomenon has been reported by Darrow (174, 175, 176) and his collaborators, namely, an association between cessation of activity in the parasympathetic supply to the blood vessels of the brain and the slow waves that appear during hyperventilation. Experiments in cats indicate that, during hyperventilation slow waves increase if the great superficial petrosal nerve is sectioned and decrease if the peripheral stump of this nerve is stimulated. Atropine and prostigmine gave confirmatory results.

Thiesen (177) reports that emotional excitement causes no specific or dramatic changes in the electroencephalogram. The most common response observed was a decrease in amplitude of beta activity in the frontomotor region.

Chemical Composition of the Nerve Cell Environment

Earlier work as well as recent studies (178, 179) have emphasized the importance of oxygen, sugar, and carbon dioxide for maintaining the electrical activity of the cortex.

Oxygen.—Cerebral anoxia and cerebral anemia ordinarily cause slow waves and then flattening of cortical activity (180). This occurs with a critical rise in cerebrospinal fluid pressure (181, 182) in orthostatic hypotension (183), after occlusion of cerebral blood vessels (184, 185), and in some cases of hyperactive carotid sinus reflex (183), not, however, in the central type of carotid sinus reflex hyperactivity, where loss of consciousness supervenes without a fall in blood pressure. The slow activity which is especially marked when low oxygen mixtures are breathed is in part at least produced by the associated acapnia (21, 186). If this is prevented by adding carbon dioxide to the inspired air a decrease in amplitude and loss of consciousness occurs without evident slowing (186). Gellhorn has shown that low sugar increases the effects of low oxygen (187). Increased metabolism also increases sensitivity to oxygen lack (188).

Sugar.—Lowering the blood sugar tends to result in a more ex-

treme response to overventilation (189). It appears that persons who are likely to show extreme slowing with overventilation are likely to show high voltage slow activity with only a slight reduction in blood sugar level (190). The findings of Davis & Wallace (189) that a moderate fall in the blood sugar sensitizes the subject to overventilation has a confusing sequel in the observation of Gibbs, Lennox & Gibbs (191) that, with very low blood sugar levels, a subject may be resistant to overventilation.

In Addison's disease, which is associated with disorders of carbohydrate metabolism, high voltage slow waves are commonly encountered (192, 193). Patients with this disease reveal an abnormal sensitivity to hyperventilation which is increased by lowering the blood sugar level (193). Low blood sugar in cases of islet cell tumors of the pancreas with attendant hyperinsulinism is associated with electroencephalographic abnormality (194). Gellhorn states that, in dogs without adrenal cortex, convulsions counteract hypoglycemic lack by increasing cerebral blood flow (195).

Carbon dioxide.—The experiments of Lubin & Price (196), in which they recorded the electrical activity of the cortex while injecting various acid and alkaline substances into the blood stream, indicate that it is impossible to show a fixed relationship between cortical frequency and carbon dioxide tension in the blood. The question remains, however, as to whether there is a close relation between carbon dioxide in the brain and cortical frequency.

Electrolytes—Rubin and his collaborators (197) have attempted to modify the electroencephalogram by increasing the concentration of certain electrolytes. Increases in calcium and potassium that were tolerated by the intact animal were without demonstrable effect on the electroencephalogram. High levels of magnesium, however, caused slowing of cortical waves. With low calcium levels encountered in parathyroid insufficiency, slow waves and scattered single spikes were seen and an exceedingly great sensitivity to hyperventilation developed (198). Thiamine deficiency has been found to cause electroencephalographic abnormality in pigeons (199) and chicks (200).

Drugs.—Convulsant drugs or stimulants (125, 127, 129, 201, 202) in convulsant or near convulsant doses (118, 203) produce either high voltage single spike-like discharges or self-sustained discharges with subsequent slow activity. Acetylcholine and choline-like substances act as convulsants (204, 205) when applied to

the cortex. The same is true of sulphathiazole (206, 207). The changes produced by convulsants and anesthetics in unsustained responses have been referred to in the section on "induced unsustained responses" and the local effects of strychnine under "induced sustained responses." Acetylcholine injected intravenously causes heart block before causing cerebral symptoms (208). Injected into the carotid artery of epileptics with petit mal, it increased the amount of wave-and-spike activity (209, 210). Indole causes convulsive discharges in lower centers before it affects the cortex (211). Caffeine spikes like those seen in frogs have also been reported with high doses of caffeine in dogs (203). Dial prevents spread of seizure discharges and chloralose facilitates spread (116). According to Adrian, the latter drug makes the cortex respond like a simple reflex mechanism (77). Depressants (33, 212 to 218) cause slowing of the electrical activity of the cortex which may not be very pronounced when compared with the marked changes in behavior that occur. Sudden withdrawal of barbiturates can cause convulsions (219), perhaps an extreme example of overshoot, such as is evidenced in some cases on recovery from the intravenous administration of large doses of barbiturates (33).

Stimulants increase the frequency of all cortical components and depressants produce a general slowing of cortical activity (33). Although drugs of the same class have the same general effect on frequency, they have specifically different effects on amplitude and are further differentiated by the particular frequency range in which their effect is maximal. An initial change produced by most depressants is an increase in amplitude of activity in the 15 to 25 per sec. range, which might be described as an increase in fast activity; but this is paradoxical for these waves, like the fifteen per second waves seen in sleep, are produced by the slowing of still faster frequencies.

Feitelberg & Pick (220) report that in frogs, doses of curare sufficient to produce muscle paralysis also produce slow activity and extreme flattening of the electroencephalogram which they interpret as evidence of narcosis. However, in man, curare is reported to cause no significant changes in the electroencephalogram (221) and comparable results have been obtained by Girden (222) with erythroidine in dogs.

Temperature.—Nims and his collaborators have studied the seizure discharges that commonly occur in dogs after freezing the

cortex (223). Stone, Marshall & Nims (180) report that a localized lesion produced by extreme cold is associated with evidence of disturbed cerebral metabolism at points distant from the lesion (165). Mention has been made already of the use of heat to destroy the outer cortical layers (81). Fever therapy in general paresis is followed by a return towards a more normal EEG in those cases that are clinically improved (225). During fever therapy, high voltage slow waves appear in the electroencephalogram (226); these are related to the acapnia that tends to develop in association with high fever (227). Heat narcosis in the frog's brain is described by Feitelberg & Pick (224); immersion of a frog for ten minutes in water at 38 to 40° C. causes an extreme decrease in amplitude of brain potentials. Recovery occurs in approximately fifteen minutes. Prior to recovery, waves with a frequency of 15 per sec. appear in bursts.

Improvement in Technique in Methodology

Two new instruments have been described that may prove valuable. Grey Walter (228, 229) has developed an analyzer that superimposes on the EEG a record of the alternating current voltage in four frequency bands. It is superior to the Grass analyzer in that it makes immediately available a plot of frequency against amplitude. It registers frequency, however, in terms of fairly coarse bands instead of in terms of fractions of a cycle per second as does the Grass analyzer. An encelphalophone has been described by Furth & Beevers (230). With this instrument, the ear rather than the eye is used to study the electrical activity of the cortex. Although the ear is a highly efficient mechanism for analyzing frequencies and frequency differences, general experience has indicated that for scientific purposes a visible record is superior to an audible one. A method has been described for turning a line record into a shadowgram (231). The criteria for selection of an electroencephalograph have been considered by Max, Wiesner & Bullowa (232). They show that one instrument tested had a cut-off close to 30 per sec., and another was sensitive to temperature changes. They fail to emphasize that so low a cut-off is highly disadvantageous and they say nothing about the extent to which the instruments tested were free from sways due to fluctuations in line voltage.

Two types of wave indices (233, 234) and a frequency spectrum

obtained by counting the waves in a given length of record (178, 179) have been advocated as quantitative methods of tabulating and presenting data. Cohn (235) has suggested the use of a frequency analyzer such as is employed for the study of tree rings. Extensive experience with the Grass analyzer has led to the conclusion that for general purposes any derived factor is less satisfactory than the original record. Some discrimination is lost as soon as a part of the electroencephalogram is discarded. Quantification is necessarily coarse, for changes are multidimensional. The inter-relation between amplitude frequency and phase is so complex that a good human eye and brain are the best analyzer available and the best index is a statement of similarities or differences noted by an experienced observer. However, where a relation can be brought out between one aspect of the EEG and a given variable, it is certainly desirable to do so, but it must be emphasized that no simple index will serve for all conditions and all purposes. Complex indices and derived expressions can be more cumbersome than the original record.

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CONDUCTION AND SYNAPTIC TRANSMISSION IN THE NERVOUS SYSTEM

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This chapter deals with literature reaching our libraries during the year preceding September 1, 1944, omitting a few papers reviewed last year. For earlier work the reader is referred to the reviews by Lloyd (1, 2) and by Renshaw (3).

The recent rapid advance in the study of synaptic conduction has been abruptly checked by the diversion of many workers in the field to more pressing problems. In the case of peripheral nerve the center of interest has shifted from the mechanism of conduction to that of regeneration. Yet a number of papers have appeared which deal with effects of high frequency currents, polarization, influence of active upon adjacent inactive fibers, and with the chemistry of nerve.

Irritability of nerve.—In single fiber preparations of the toe nerve of the green frog recorded at the site of electrical stimulation, Schoepfle (4) finds the height of the shock artifact remains constant as threshold current duration decreases and imposed voltage increases. This implies, as Bishop has suggested, that a nerve fiber will fire when the applied voltage across some element of the nerve attains a critical value regardless of the rate at which voltage increases. Rössel (5) has determined impedance, reactance, and threshold at various frequencies on the frog's sciatic nerve before and after removing the epineurium. After removal of the sheath, total polarization decreases, reactance drops to between a third and a tenth, and impedance to two thirds of the former values. The threshold is increased. Calculation of the amount of electricity stored at threshold by polarizable boundaries shows that its magnitude and dependence upon frequency are little altered. Schwartz (6) has studied the changes in irritability that follow stimulation of nerves in man at frequencies ranging from 10 per second to 36,000 per second applied for five minutes. The threshold is raised for several minutes, then returns to the original level or below it. When the test current is of the same frequency as the conditioning current, the changes in threshold are greatest at 200 per second.

After stimulation at from 20 to 200 per second the threshold is greatly raised for test currents of similar low rates but little altered for high frequencies. The results are compared with those obtained in Hill's laboratory. They are attributed to selective excitation of different fiber groups.

The influence of active fibers upon the irritability of adjacent inactive fibers has been the subject of two recent thorough investigations. Marrazzi & Lorente de Nó (7), employing the sciatic nerve of the frog, find an early series of changes opening with a brief depression immediately preceding the spike potential. During the rising limb of the conditioning action potential this is sharply interrupted by enhancement which promptly fades into a second depression. This rapidly alternating cycle is often succeeded by a more prolonged lowering of threshold beginning after the termination of the conditioning spike potential and associated with a decreased membrane potential in the test fibers. In a similar study employing the cat's peroneal nerve Rosenblueth (8) describes a series of changes in threshold differing somewhat in their early phase relations from those just described. Such divergence in results obtained with entirely adequate techniques emphasizes the importance of a point stressed by Marrazzi & Lorente de Nó. They find that the form of the early portion of the interaction curve may be altered by moving the test stimulus electrodes close to the point of bifurcation of conditioning and test fibers. They believe that the shape of the curve depends upon the geometric relations of the two sets of fibers, relations which determine the direction of flow of action currents through the inactive axons. They voice a timely warning of the impossibility of prediction concerning the pattern of changes in irritability in synaptic regions of the central nervous system resulting from activity in adjacent units. Rosenblueth has analyzed the later phases of interaction by the use of veratrine and of potassium chloride. They are not affected by either anodal or cathodal polarization of the stimulated region and they do not invariably parallel the after potentials. He suggests that the early phases are due to electrical, the late ones to chemical factors among which he implies that the potassium ion may be included.

In a second paper (9) Rosenblueth describes recruitment in the peroneal nerve of cats observed after intra-arterial injection of veratrine. The underlying process may be long enduring. Its time course does not parallel that of the negative after potential.

It is not influenced by change of site of stimulation during the course of a train of stimuli and hence is determined by conducted responses. These may be either in the fibers tested or in others adjacent to them.

Bentley & Schlapp have studied the effects of limiting the blood supply (10) and of applying pressure (11) to the peroneal nerve of the cat. They conclude that a small blood supply is essential, but that the normal circulation affords a wide margin of safety. They distinguish block due to pressure from that due to ischemia and state that the former is slower in onset and far slower and less complete in recovery. They associate failure of recovery with damage to vessels at the margins of the pressure block where deformation of tissue is severe.

Physicochemical factors.—Steinbach, Spiegelman & Kawata (12) have measured rectification in the giant axons of the squid, employing brief direct current between an injured end in isotonic potassium chloride and an uninjured point in a test solution. The resistance is lower when the cathode is on the uninjured region. Potassium in low concentration has little influence on rectification but reduces the injury potential considerably. In concentrations above that in sea water it also induces a drastic fall in rectification. Calcium in wide range has little effect upon the injury potential but more than doubles the rectification at concentrations two to three times that obtaining in sea water. Excess of calcium prevents the drop in rectification from excess potassium but has little effect upon the fall in injury potential. They regard rectification as a better measure of membrane stability than the injury potential. Guttman reports a similar decrease of rectification from potassium and also from a number of narcotics, but obtains no effect from calcium or barium in concentrations up to 0.083 *M* (13). Steinbach & Spiegelman (14) have determined the content of sodium and potassium in samples of axoplasm extruded from single giant axons of the squid. Isolation of the axon from the animal is associated with loss of potassium and gain of sodium. In solutions with low concentrations of potassium, sodium enters the axoplasm and potassium leaves it. With high concentrations the direction of exchange is reversed.

Shanes (15) has analyzed the effect of high concentrations of potassium on the aerobic fraction of the injury potential of frog nerve. Depression of the total potential is a linear function of the

logarithm of the potassium concentration of the medium. The aerobic fraction of the potential is suppressed by potassium in the same manner as is 50 per cent of the oxygen consumption. He regards these results as consistent with the theory that the maintenance of a specific phosphorylation is responsible for the injury potential.

Wyss (16) has determined the thiamine content of frog sciatic nerves, using a refined thiochrome method for free, and the manometric method of Atkins, Schulz, & Frey for total thiamine. He obtained mean values of 1.2 μg. free and 3.5 μg. total thiamine per gm. of nerve. Von Muralt & Zemp (17), using a biological assay, have studied the effect of stimulation upon the content of free thiamine in frog sciatic nerve. Stimulation increases the value by as much as 2 μg. Von Muralt (18) finds that on mild oxidation of nerve with ferricyanide in an alkaline medium thiamine is changed to thiochrome and longitudinal or cross sections of nerve show an intense violet fluorescence of the myelin sheaths. In degenerating nerves of guinea pigs, a decrease in thiamine content can be detected by this method within twenty-four hours after section. By passing a constant current of 0.1 to 0.5 ma. for 10 min. through nerve he confirms Bethe's finding of polarization pictures. In histological preparations of such nerves, the absorption of toluidin blue is increased at the former anode, decreased at the cathode. Thiochrome fluorescence is more intense at the anode.

Lorente de Nó (19) finds that concentrations of choline or acetylcholine up to 0.1 *M* (which maintains osmotic equilibrium of the fibers) neither depolarize frog nerve nor block conduction in it. During anoxia and subsequent recovery, their action resembles that of magnesium ions.

Regeneration of nerve.—Berry, Grundfest & Hinsey (20) have compared the structural with the functional state of regenerating fibers at various intervals after section and primary suture of the tibial, peroneal, and saphenous nerves of cats. Action potentials occur as early as the seventeenth day after operation. These are small and are conducted at less than 1m. per sec. At longer intervals the potentials increase in size, velocity, and complexity, showing two prominent groups in addition to a C wave. Thresholds for electrical stimulation are high peripheral to the suture and low central to it. The most rapid distal fibers are not necessarily projections from the most rapid central fibers. Progress in return of

conduction velocity distal to the suture is slow and velocity increases at a constantly decreasing rate with respect to time. Even at 466 days it is less than 80 per cent of that of the controls. Recovery of maximum fiber diameter follows a similar course. Relationship between maximum conduction velocity and maximum fiber diameter in the regenerating nerve is approximately linear.

The role of the peripheral stump in the control of fiber diameter has been exquisitely clarified by Sanders & Young (21). The peroneal and tibial nerves of the rabbit divide into branches to muscle with large fibers (bimodal in distribution with peaks at 3 and 15 μ) and branches to skin which do not include such large fibers. One year after end-to-end suture of the peroneal nerve, and ten months after cross union of peroneal and peripheral stump of tibial, the motor funiculi contained larger fibers than did the cutaneous branches. The largest fibers in both divisions were smaller than in normal nerve and the motor distribution was no longer bimodal. In a case in which the peroneal was crossed with the peripheral stump of the tibial, which had been denervated for eighteen months, the motor funiculi contained larger fibers than did the cutaneous branches after ten months of regeneration. Yet the fibers were smaller than in the cases of immediate cross union and again the motor fibers showed no trace of bimodal distribution. After twenty-five days of denervation the Schwann tubes still reflected in their caliber the differences in diameter of their former fibers. This was still true after fifteen and a half months although the tubes were now smaller. When the nerve was not cut but merely crushed, regeneration was more successful, the bimodal distribution of the motor fibers even being restored. The results indicate that Schwann tubes not only reflect the caliber of their former units but limit that of the regenerating elements that they enclose; In the absence of this influence the potential diameter of a regenerating fiber is determined by the size of the axon from which it arises. Delay of suture results in small, poorly medullated fibers because of shrinkage of the tubes of Schwann.

Weiss and his associates have continued their ingenious development of methods of repair. They report full functional recovery in cats and in monkeys after bridging nerve gaps of several centimeters with grafts of frozen dried nerve stored several months and rehydrated for use (22). Optimal results are obtained after direct reunion with sleeves of frozen-dried artery in rabbits, cats,

and monkeys (23). Should the arterial sleeve be too tight, however, the regenerating fibers are defective in both diameter and myelinization (24). With nerves grown *in vitro* compression delays but does not prevent Wallerian degeneration. This effect is due to compression, not to oxygen lack nor to isolation from culture media (25).

Reunion of severed nerves by cuffs of tantalum foil fashioned into resilient self sealing tubes has given promising preliminary results (26). Poth & Bravo-Fernandez suggest that amputation neuromata may be prevented by encasement of the severed nerve ends in rigid tubes (27).

Receptors.—In two important papers Bishop has continued his studies reviewed last year (2) on stimulation of pain receptors with electric sparks. The first (28) deals with the isolation of pain spots by anesthesia of a nerve branch. In the region of overlap with functioning branches, individual pain spots are surrounded by anesthetic areas, which permit the estimate of the area supplied from a single point and hence the degree of overlap of such centers in normal skin. Sensitivity diminishes progressively to the periphery of such an area. The region of overlap of adjacent spots is small and minimal in sensitivity. If two such units are stimulated synchronously or by alternate bursts, two point discrimination between them depends upon both strength and frequency of stimulation: the closer the spots tested, the stronger or the higher is the rate of stimulation required for their separate recognition. Two points discriminated as such do not summate in painful sensation but usually do so if not differentiated. Some adjacent points mask each other. They neither summate in intensity nor are they recognized as separate spots.

From a single point differences not only of intensity but also of rate and duration of stimulation induce qualitative differences in sensation ranging from touch with a slight after-itch to persistent itch, prick, and pain. Most observers will agree with the author's conclusion that these results "point to a central qualitative interpretation of sensory impulses depending only on quantitative factors involving identical peripheral mechanisms within the single modality of pricking pain."

The second paper (29) deals with the structural identity of the pain spot. After removal of skin to various depths by chemical or surgical means, the denuded areas were studied before and during

regeneration of their end-organs. Epithelium regenerates from the base of each hair follicle before sensory endings are restored. A nerve twig containing pain fibers grows toward a group of from one to three follicles and is distributed within an area containing a single pain spot. Many follicles contain no hairs. The most sensitive point may be correlated with its position immediately over the nerve twig. "Dendritic fibers" derived from connective tissue appear shortly before the arrival of the nerve twig.

Granit has continued his study of the mammalian retina using single fiber preparations (30). In the pure rod retina of the guinea pig nearly all units discharge at the onset of light. Some stop abruptly at the end of stimulation, others show after-discharge. In the mixed retina of the cat, on the other hand, most fibers respond at both "on" and "off." Pure "off" elements are rare in both species. In both, spontaneous activity is common and offers a background for the demonstration of inhibition. Post-excitatory inhibition occurs in all types of fiber. Pre-excitatory inhibition, best seen in the pure "off" response, has a briefer latency. It coincides with the active negative component, PIII, of the electroretinogram. Wulf & Jahn, studying visual diurnal rhythm in beetles, note that during the day the electroretinogram is simple; during the night, simple at low intensities, complex at high ones (31).

Spiegel has observed a depressant effect of cold upon the static receptors of the labyrinth (32). In decerebrate cats a U-shaped cannula was inserted in the outer and middle ear and perfused with water at temperatures ranging from 3° to 20°C. Temperatures of 9° or lower decrease muscle tone of the homolateral and sometimes also of the contralateral foreleg. The effect is reversible. Similar but less pronounced effects were obtained on intact rabbits in the supine posture. In unanesthetized rabbits and in cats under bulbocapnine, the cannula was perfused for several minutes and then quickly withdrawn to avoid any influence of its weight on posture. The animals assumed the attitude characteristic of unilateral labyrinthectomy, the head rotated with the perfused ear down. Bilateral perfusion caused no significant change in post-rotational nystagmus. Hence the depressor effect appears to be confined to the gravity receptors.

Spiegel, Oppenheimer & Wycis have studied the labyrinthine receptors concerned in vasomotor reactions to rotation (33). In cats with puncture of the round window rotation about the longi-

tudinal or the dorso ventral axis induced a fall in blood pressure but no nystagmus. Injection into the labyrinth of 2 per cent cocaine in alcohol temporarily abolished the vasomotor response. In centrifugalized guinea pigs during the stage of paralysis of postural labyrinthine reflexes, rotation induced a fall in blood pressure. These experiments seem to indicate that the vasodepressor reflex originates in both types of labyrinthine receptors.

Zotterman has recorded a microphonic effect from the macular region of the saccule and also impulses from its nerve in the pike and the burbot (34). In both instances bursts of activity were synchronized with the tuning fork. Responses to rotation were obtained from the nerve of the posterior ampulla during acceleration when the ampulla was leading and on deceleration when trailing its canal. Spontaneous activity was rarely met and was not inhibited by rotation.

Clear evidence of peripheral inhibition has been presented by Galambos in an important research upon impulses in single fibers of the auditory nerve (35). Either spontaneous discharge or that set up by a tone or noise may be reduced in frequency or stopped by a second tone or noise. The inhibitory tone may be higher or lower than the excitatory and may even be a tone which excites when presented alone. The inhibitory action of low tones upon the activity due to high ones is especially widespread. The tones which inhibit single nerve fiber activity in the cat have the same general distribution as those which are most effective masking tones for man. The mechanism of the effect is not known. Mechanical and electrical factors in the middle and inner ear appear to be excluded. It is suggested that spiral bundles of nerve fibers underlying the organ of Corti may mediate the inhibition.

Sympathetic ganglia.—Eccles' important work on synaptic potentials was reviewed last year (2) and is mentioned here merely to supply a bibliographic reference to a paper then in press (36).

Kuntz & Saccomanno (37) have presented both anatomical and physiological evidence that certain intestinal reflexes are mediated by sympathetic ganglia after severance of all connections with the central nervous system.

Inhibition in the spinal cord.—Martini, Gualtierotti & Marzorati (38) report the complete inhibition of the cat's spinal cord below the level of stimulation by passing through a spinal segment rectangular currents of from fifty to seventy ma. at 280 per sec.

They state that the effect does not occur if the cord be transected or frozen above the segment stimulated and is, therefore, mediated through a higher center which they localize in the ventral part of the diencephalon near the corpora mammillaria.

Ging-Hsi Wang & Tse-Wei Lu have studied the reflex response to touch in frog embryos (39). The duration of the response decreases from more than four seconds at 2 mm. body length to one and a half seconds at 4½ mm. At this stage, transection of the cervical cord or destruction of the rostral half of the hind brain lengthens the response to its primitive duration. They attribute this effect to inhibition mediated by impulses from the hind brain.

Van Harreveld *et al.* have continued the analysis of the effects of asphyxiation of the cord (40, 41). At the beginning of asphyxia reflex activity is increased. The flexion reflex persists longer than the knee jerk. The knee jerk may be inhibited up to the time of its disappearance. Cooling the cord reduces greatly the rate of injury by asphyxia.

Supernormal phase in somata of motoneurons.—Hoff & Grant (42) have analyzed the double responses occasionally met in single unit records from muscles during the stretch reflex. These were recorded with concentric needle electrodes from soleus and triceps in decerebrate cats. The occurrence of doublets was greatly increased by veratrine and by lowering either pH or body temperature. The first two procedures are known to increase negative after-potential and supernormal phase in nerve fibers. Tripling and quadrupling were occasionally met, most frequently with the use of veratrine. The interval between paired responses usually lay between 3 and 5 msec., and rarely exceeded 20 msec. The agreement with the time relations of supernormality in A fibers is striking. Triceps units were far more prone to double responses than were those of soleus. Such a difference between motoneurons so closely allied in function inclines the authors to a timely warning against considering any one neuron as a "sample" neuron.

Integration of reflex patterns.—Harris, Hodes & Magoun have traced the intramedullary path of the pupillodilator reflex in response to stimulation of the sciatic, splanchnic, and trigeminal nerves (43). It is distinct from the lateral spinothalamic tract throughout its course. Hence they suggest that pupillodilatation and pain evoked by stimulating afferent nerves bear only a coincidental relation to each other.

Beritoff reports various patterns of response from stimulation of lumbar dorsal roots in acutely spinal cats (44). He finds that repetitive stimulation of L4 or L5 excites extensors of the knee; of L7 or L8, flexors of the knee; of L6, either, or both groups together. Intense stimulation yields cocontraction of these antagonistic muscles. With moderate currents single shocks induce cocontraction, repetitive volleys reciprocal innervation. He reports inhibition lasting ten seconds from a single shock and increasing with the frequency of repetitive volleys. He obtains inhibition from stimulation of ventral roots. He notes the familiar occurrence of facilitation following inhibition and stresses its relation to rebound. Extensor responses from L4 and L5 recall the observation that in the acutely spinal cat the skin on the lateral aspect of the thigh is a receptive field for ipsilateral extension (45). Cocontraction from a single shock replaced by pure flexion from repetitive stimulation at the same strength is reminiscent of a possibly related result. A pure extensor response to a single shock of a strength, which in repetitive form yields only flexion, has been observed (46) in connection with sciatic stimulation in the decerebrate. These reversals may well be related to the recruitment of pain sensation reported by Bishop (28). Many observers will incline to attribute the frank cocontraction on strong stimuli to spread of current. On the other hand, a small extensor component in a dominantly flexor response is well known (47, 48) again as a decerebrate pattern. The combination of a small extensor contraction, low in threshold and changing little in size on increase of strength of stimulation, with a flexor response graded in proportion to the stimulus has been seen frequently with single shocks to lower lumbar roots in the spinal cat (46). It should probably be attributed to firing of the monosynaptic arc of the stretch reflex (49 to 52) before it can be inhibited through internuncial activity.

We have just considered some of the reflex complications resulting from simultaneous stimulation of heterogeneous fiber groups. In this connection Gordon has presented strong evidence that, in the vasomotor reflexes obtainable from the tibial nerve of the cat, the pressor response is mediated by small fibers, the depressor by large (53). At low frequency, weak shocks induce a fall of blood pressure, strong ones a rise. Cocaine applied to the nerve proximal to the point of stimulation abolishes pressor before depressor responses. On the other hand, cold or asphyxia eliminates

the depressor and enhances the pressor reflex. If the strength of stimulation be constant, reversal from a depressor to a pressor response may be induced by increase in frequency. Again we are reminded of Bishop's work on pain spots (27) discussed on page 460. The same relation is illustrated in the field of skeletal reflexes by Croisier (54) who has recorded the responses of the crural triceps of the frog to stimulation of the ipsilateral sciatic nerve by repetitive condenser discharges. Low frequencies induce sustained contraction, medium frequencies an initial contraction inhibited during the period of stimulation, high frequencies a still briefer response, promptly eclipsed and often followed at the end of stimulation by rebound. Thus the reflex correlates of pain show recruitment similar to that which occurs in terms of sensation. Hence it seems probable that this feature of the pain pattern is integrated at the spinal level.

Gesell & Atkinson find multifiber summation more important than change of frequency in grading contraction of the diaphragm in the mouse, rat, rabbit, dog, and horse (55). Frequencies are higher in the smaller animals.

Petitpierre reports reflex alteration of phrenic discharge from resistance to respiration (56) and from section of the other phrenic (57) after section of the vagi, the cervical sympathetics, the third to eighth dorsal cervical roots, and the spinal cord at the eighth cervical segment in rabbits and cats. He concludes that the remaining afferent path must traverse ventral roots.

Skoglund & Uvnäs (58) have recorded reflex discharges in dorsal roots of cats from constant currents of sufficient strength to cause maintained repetitive afferent discharge and from repetitive stimuli varying in shock duration, rate of rise, and frequency. With brief repetitive shocks, the reflex is sustained longer at low frequencies than at high. Slowly rising currents are less effectual. They confirm Barron & Matthews (59) in finding the response enhanced by lowering the temperature of the cord, and Toennies (60) regarding its latency of a length indicative of synaptic transmission.

Ebbecke (61) describes reflex swallowing in man from immersion of the face in cold water and notes facilitation between this response and that obtained from the mouth.

Other interesting papers (62 to 66) deal with aspects of reflex problems too remote from our subject for individual comment here.

Myelination and conduction in central pathways.—Ulett, Dow & Larsell have followed the development of conduction in the corpus callosum and the corticopontocerebellar pathway in young rabbits (67). In both cases latencies were shorter in the older animals and in both tracts conduction began several days before myelination.

Potentials in dendrites.—O'Leary & Bishop have correlated potentials recorded from various depths in the optic lobe of the duck and the goose in response to single shocks to the optic nerve with the cytoarchitectural layers concerned (68). In spite of clear stratification of cells and fibers, the dendrites of individual cells extend through several layers toward the outer surface. Potentials lasting several milliseconds are attributed to enduring negativity in these dendrites.

Chemical factors in synaptic transmission.—Prosser has analyzed the action of a large number of salts upon the activity of the abdominal ganglia of the crayfish (69).

Feldberg has studied the synthesis of acetylcholine in sympathetic ganglia and in cholinergic nerves (70). The superior cervical ganglion, cervical sympathetic, vagus, and phrenic nerves, and motor roots, cut into small pieces and incubated one to two hours in buffered saline with physostigimine, all synthesize acetylcholine apparently to restore its original concentration in the tissues after its release. Sensory roots do not. If the cervical sympathetic be cut, the distal part of the nerve and the superior cervical ganglion lose the capacity for synthesis of acetylcholine in about two days. This loss occurs coincidently with the great drop in acetylcholine content, for which it is considered responsible, and with impairment and loss in synaptic transmission. Feldberg concludes that synthesis of acetylcholine in ganglia is a property of preganglionic endings and is a necessary preliminary for normal sustained synaptic transmission.

Bülbring, working with the perfused superior cervical ganglion of cats, notes modification of the response to stimulation of the cervical sympathetic following epinephrine (71). Contraction of the nictitating membrane is increased by small doses, decreased by large ones. The increase is observed only with submaximal stimulation at low rates. The response to acetylcholine injected into the perfusion fluid is similarly affected by epinephrine. During prolonged preganglionic stimulation, the perfusate collected from the

vein contains an epinephine-like substance which was assayed by both biological and chemical methods. Concentrations similar to those so found, enhance synaptic transmission when injected. They also cause vasoconstriction in the ganglion, but this is more evanescent than the facilitation. Chromaffine cells found in the ganglion are suggested as a source of the epinephrine. A possible mechanism for these effects is suggested by the work of Torda & Wolff (72). They report that epinephrine in concentration $1:10^{-8}$ increases the synthesis of acetylcholine *in vitro* by from 40 to 250 per cent. They attribute the result to epinephrine's property of forming a reversible oxidation-reduction system.

Nachmansohn & Hoff report a significant decrease in cholinesterase content of the cord following section of dorsal rests (73).

Observations continue to accumulate upon the influence of acetylcholine introduced in various ways and dosage on the activity of the nervous system. Miller has applied it in dilutions of from one to fifty million to one to one million to the floor of the fourth ventricle over the hypoglossal nucleus in decerebrate cats which had received 0.25 mg. of physostigmine sulphate intravenously (74). He observed furrowing and gross movements of the tongue and swallowing after latencies of four to fifteen seconds. The effects were abolished by atropine. Calma & Wright (75) injected 25 to 100 mg. intra-arterially in decerebrate cats and observed increased tone in the quadriceps muscle. Gesell & Hanson (76) report respiratory changes in dogs following acetylcholine or physostigmine. Breathing becomes dominantly costal and expiratory. The effect is abolished by atropine. Beritoff & Nivinskaja (77) note a depression of the flexion reflex in the frog. Beritoff reports enhancement of crossed reflexes after application of acetylcholine to the dorsal surface of the cat's cord (44). Armstrong (78) contrasts the turtle, whose iridoconstrictor has a relatively high threshold for acetylcholine and can be paralyzed by enormous doses, with amphibians in which the response is far more sensitive. He suggests that there may be two types of cholinergic terminations: one with high concentration of cholinesterase where acetylcholine may have "nicotine" effects, the other having little or no cholinesterase where the drug has "muscarine" action.

Kuffler has investigated the effects of lack and of excess of calcium upon the neuromyal junction, employing the frog's sartorius and isolated fiber preparations from the adductor longus

(79). Reduction of calcium affects the endplates prior to the nerve endings and muscle fibers and it is at the endplates that spontaneous activity originates. Here the sensitivity to applied acetylcholine increases 100 to 1,000 times. Subsequently neuromuscular block develops although the nerve endings still conduct impulses and the action potential of muscle from direct stimulation is not appreciably altered. It is suggested that the block is due either to diminished production of the "transmitter" or to diminished excitability of the endplates. The portion of sartorius immersed in calcium deficient solution becomes negative to the rest of the muscle. Excess of ionized calcium gradually blocks transmission, presumably by lowering the excitability of the muscle fibers.

The role of chemical reactions, including those involving acetylcholine and thiamine, in central excitation is also considered by Schmidt in the chapter on Respiration (p. 231) in this volume.

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THE SOMATIC FUNCTIONS OF THE NERVOUS SYSTEM

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I. INTRODUCTION

During the three year period between July 1941 and July 1944 the literature on the somatic functions of the nervous system shows wide developments. Many trends of investigation of this period have been dependent on the war and because of this the field is materially different from what it has been in the past. The amount of literature has decreased because of both paper and manpower shortage. Much physiological research has been directed into such practical channels as have been dictated by the needs of the present emergency. It is noteworthy, however, that the caliber of the material has not on the whole degenerated although haste, urgent practical need, and the deflection of some of the best minds from research to more active service might have been expected to have had that effect. The very high standard of the English publications in this field are particularly gratifying. In the opinion of the author the standard in this country has not remained as high.

An attempt has been made to limit the scope of this chapter to pure physiology of the somatic nervous system, partly because there is ample material within this subject to fill the space allotted for this chapter and partly because some of the other material is highly specialized and will be dealt with elsewhere either in the present volume or in subsequent ones. Thus, the effects of high altitude flying and of fatigue which have become subjects of much physiological study and speculation, the neurophysiology of head injuries, and the study of peripheral nerve injury which have lead to significant findings on degeneration and regeneration have been omitted. Many somatic functions of the nervous system are dealt with in part in other chapters in this volume: on brain potentials; on synaptic transmission; on respiration; and on physiological psychology.

On reviewing the material for this chapter it has become apparent that in addition to the effect of war, two other factors have influenced the developments in neurophysiology during the past

three years. The first is the use of more accurate experimental methods notably in the neurosurgical procedures and in the use of electrical apparatus for stimulation and excision. With this improvement in techniques, the second trend has become evident, namely that the field of physiology as related to the somatic nervous system has been extended and its boundaries have become so intermingled with those of other fields that they are often indistinguishable. Today it is often difficult to find articles dealing purely with the anatomy of the nervous system and some of the best functional discussions are found in the anatomical journals. In addition, due to observations on fatigue and on battle conditions, the boundary line between autonomic and somatic function has become less well defined than many would have thought possible, particularly in relation to corticoautonomic and hypothalamic activity. The war has also led to much interest in the frontal lobes. Symptoms resulting from lobotomy and shock therapy and various facts produced by work on experimental neuroses have become inseparably integrated with the more concrete and simpler somatic motor functions of the cortex. Finally, there has been much published from the clinical field in relation to aphasia, apraxia, and allied disorders of the more complex motor acts which is of neurophysiological significance.

Reviews.—This period has produced an unusually large number of reviews on various aspects of central nervous system function, many of which will be noted later under their particular headings. The second edition of Fulton's *Physiology of the Nervous System* (1) brings up to date the textbook material on the subject. Morgan (2) deals with much the same subject matter. The neuroanatomies of Krieg (3) and of Mettler (4) discuss in detail the modern concepts of physiology. Walshe's neurology (5) also handles neurophysiological material. The study of pain has produced three reviews: that of Sir Thomas Lewis (6), that of Livingston (7), and the volume of the *Association for Research in Nervous and Mental Disease* for 1943 (8).

On the motor side the volume of the same association for 1942 is on *Diseases of the Basal Ganglia* (9), and a volume edited by Bucy and entitled *The Precentral Motor Cortex* (10) has been put together by a number of authors. In the field of the frontal association areas two volumes by Cobb (11, 12) contain a great deal of neurophysiology.

Finally, as a background for all neuroanatomical or neurophysiological research, the atlas of Riley should be recommended (13). In it there are detailed microphotographs of every section of the cord with attendant identification of tracts and nuclei. There are similar sections cut in horizontal, frontal, and longitudinal planes through the cerebrum. These are all stained by the Weigert technique and the whole is more detailed and complete than any previous atlas of neuroanatomy.

Because of the nature of the published material it has seemed best to divide this chapter into four sections as follows: (*a*) Sensory function, (*b*) Motor function, (*c*) Cortical function, and (*d*) General problems of organization, development, and recovery of nervous tissue.

II. SENSORY SYSTEM

The sensory functions have had a relatively large share of investigation because many objective methods for tracing the course of afferent impulses have been discovered.

A. Pain

The subject of pain has been considered from many aspects. Wolff (14, 15) discusses the mechanisms of headache in two articles which summarize the results of his previous work. He presents evidence that, whereas headache following histamine injection is produced by traction on the cerebral arteries at the base of the brain as they dilate, migraine is the result of changes in extracerebral arteries. The former is relieved by increase of intracranial pressure, which thereby furnishes support for the distended arteries, while it provides no such relief during migraine. Headaches induced by hypertension are likewise unaffected by increase in intracranial pressure. In the opinion of Wolff the essential migraine phenomena result from cranial vessel dysfunction. Preheadache disturbances follow vasoconstriction while headache results from dilatation and distention chiefly in the branches of the external carotid artery. It seems definitely proven that pain in the head is related chiefly to stimulation of endings in the blood vessels and that this is most often produced by changes in their diameter.

Wolff and his associates have devised an apparatus useful for measurement of pain (16, 17). A ray of light is focussed on a skin area and the intensity at which pain, as opposed to warmth, is

felt is called the pain threshold. Hardy, Wolff & Goodell (16) by this means separate the perception threshold of pain from the reaction to pain. The latter includes autonomic reactions, anxiety, fight, and flight. The pain threshold is found in normal man to be relatively constant and independent of age, sex, emotional state, and fatigue. Elevation of pain threshold occurred either as a result of organic disturbance within the nervous system or because of functional changes. Inflammation of the skin appreciably lowered its pain threshold. Otherwise lowered pain threshold was found associated only with hysteria or malingering.

Guttman & Mayer-Gross (18) in an excellent discussion of the psychology and physiology of pain reach the same conclusion as to the steady threshold to pain when objectively measured. They describe the objective signs of the quality, intensity, and localization of pain.

Gasser (19) discusses the evidence with regard to the nature of pain-carrying fibers. Using the well known fact that asphyxia blocks small medullated fibers before large ones but affects unmyelinated C fibers relatively late, while cocaine blocks first the C fibers, later the small, and then the large myelinated fibers, he has made an analysis of pain-carrying fibers. His opinion is that contrary to the law of "specific nerve energy" there is no specific axon for a given modality such as pain but that fibers belonging to each modality must be widely distributed throughout the different fiber sizes. Pain impulses, for example are carried by both myelinated and unmyelinated fibers. This opinion is not shared by Walshe (20), who, in a review of the earlier knowledge of the anatomy and physiology of cutaneous sensibility, offers only the evidence which fits with the establishment of such specific nerve function. Sensory units are postulated by Walshe as being analogous to motor units including the posterior root fibers and all end organs for a given mode. The presence of such units does not however necessitate as Walshe states that only one form of fiber conducts this sensation.

Bishop (21) has stimulated the skin in humans by high voltage, low current, spark discharges which produce discrete sensory responses, and by this means has mapped prick and touch areas. He records that there are skin units varying in size from a few millimeters to 15 mm. which respond as one unit. Within this unit there may be extremely sensitive points as well as surrounding points

which are of lower sensitivity. Prick has a much lower threshold than touch except on the balls of the fingers where touch threshold is lower. By this method Bishop has traced the distribution of prick and touch points in areas containing many receptors and those with few. Later (22) this method of stimulation was combined with that of anesthesia of small nerve branches and thereby small anatomical units were isolated within which there was but one sensitive point surrounded by those less sensitive. In spite of considerable overlap already known to exist in the subcutaneous mesh of fine nerve fibers, Bishop seems to have defined a sensory skin unit for pain both anatomically and by functional means.

In these same articles Bishop discusses itching which he finds is a sensation recorded by the pain fibers in response to low intensity, high frequency stimuli or to slow, repeated stimuli each of which causes an initial prick response. Itching is described by Rothman (23) as resulting from the same type of stimuli and as conducted by the slow C fibers. Itching also, according to this author, results as an after sensation from a variety of other stimuli. It occurs when previous injury to skin, nerve trunk, or central nervous system has been incurred and is a part of the heightening of protopathic sensitivity.

The pain which follows some amputations has been considered by a number of authors and its relation to the sympathetic system has been ascertained by its disappearance following sympathectomy. White (24) reviews the evidence concerning pain of amputation stumps and concludes that it is the result of local irritation at the end of the cut nerves where neuroma may or may not be present. The local pain, burning, and tenderness may be relieved by surgical interruption of the sympathetic outflow to that area or by section of the spinothalamic tract. Livingston, who made the first observations on the effects of sympathectomy on pain of this sort has summarized his findings in a book entitled *Pain Mechanisms: A Physiological Interpretation of Causalgia and Its Related States* (7). The same subject of sympathetic outflow and pain is discussed by Sir Thomas Lewis (6) who gives much of the detail of his work on the innervation of the skin and its capillaries. In the volume on *Pain* from the *Association for Research in Nervous and Mental Diseases* (8) will be found chapters on pain as related to the other autonomic functions, within visceral organs, a subject which is not within the limits of this chapter.

The relation of phantom limb to pain is discussed by White (24), Livingston (7), and de Gutierrez-Mahoney (25). Their conclusion that it is related to the parietal cortex will be discussed later in detail.

Weaver & Walker (26) and Walker (27, 28) have traced the spinothalamic and trigeminal tracts within the mesencephalon. The arrangement within the spinothalamic tract, traced after chordotomy or midline posterior myelotomies (29) in monkeys, is a laminated one wherein fibers from lower regions lie lateral and dorsal to those arising at higher levels of the cord. In the medulla, the fibers from cervical regions are deep in contrast to those from lower areas which are arranged peripherally. Further observations on anterior chordotomy reveal that such an operation when complete abolishes pain, shivering, girdle sensation, and itching (30).

The special subject of the mediation of pain through the fifth cranial nerve has received much attention. Walker, among others, has relieved intractable face pain by means of section of the mesencephalic root of the fifth nerve together with the spinothalamic tract at that level (31). By this method heminanalgesia and hemithermanesthesia of the opposite side of the body is also produced. Proprioceptive sensibilities are not impaired. Partial section of these secondary pain pathways in the mesencephalon gives rise to monoanalgesia. The arrangement of fibers in the mesencephalon is geographically similar to that of their final distribution within the nucleus ventralis posterior of the thalamus (28).

Weinberger & Grant (32, 33), who discuss the subject of pain from the trigeminal nerve, successfully relieve this in all three branches of the peripheral nerve by intramedullary tractotomy, sectioning thereby the descending root of that nerve. Harrison & Corbin (34), tracing stimuli by oscillographic means, have been able to follow the ophthalmic division of this nerve as far as C-1 of the cord, the maxillary division as far as the rostral portion of C-1, and the mandibular division to the junction of the medulla and cord.

B. Proprioception

The topical organization and termination of the posterior column in monkeys have been investigated. The posterior columns, as is well known, were seen to contain the most caudal fibers along their medial aspects and lamination laterally then occurred as the cord was ascended. The lower portions of the tract, lying mesially,

terminated in the nucleus gracilis; the more rostral portions in the nucleus cuneatus proprius and externus (29). Section of the medial lemniscus in chimpanzees and monkeys resulted in no proprioceptive change as indicated by the learned habit of weight discrimination. Primary section of the superior cerebellar peduncle was likewise without effect. If section of both medial lemniscus and dentatorubrothalamic tract was made together, however, a permanent loss in weight perception followed. It was suggested that the cerebellothalamic tract possessed the ability to subserve the recovery of proprioceptive function following section of the medial lemniscus (35).

Von Brücke & Early (36) investigated the synchronization of proprioceptive impulses within the spinal ganglia. But both on stimulation of peripheral proprioceptive fibers and on stretch of gastrocnemius muscle impulses were picked up from dorsal roots which were not changed in character by passage through the ganglia.

C. Vibratory Sense

A mechanical device for accurate measurement of vibration has been described and also the means of measuring threshold vibrations (37, 38). Both touch and pressure were felt to be implicated in the perception of vibration since destruction of either sense appreciably raised the threshold for its detection. No specific sense organs were found by biopsy of human material for either the sense of pressure or vibration (39). The authors suggest that the neurovascular system and its structures are implicated in this sensation on the basis of the facts that the neurovascular system contains structures which are highly endowed with nerves and that areas recording vibration were richer in these neurovascular structures than were other regions. It was suggested but without verification that arteriovenous anastomoses and glomus bodies may be implicated in the detection of vibration.

D. Vestibular Mechanisms

Adrian (40) has traced discharges from the vestibular receptors of cats into the medulla in the region of the vestibular nuclei. In these nuclei he finds focal representation of stimuli produced either statically by gravity or by stimuli which follow the movement of rotation. There is further distinct representation of various types

of rotation. Meticulous studies of the directional preponderance of nystagmus following cerebral lesions have been made also (41, 42).

E. Thalamic Function

Based, to a considerable extent, on the anatomic work of Walker (28), the literature of this period contains many anatomical notes on thalamic representation. Those with physiological implications are found in Walker's article summarizing the knowledge on the central representation of pain and Lashley's study (43) of the thalamocortical connections of the rat. Both these studies merely emphasize or further elaborate the topical representation already known to exist within the thalamus.

Dempsey, Morison, and their associates (44 to 48) in investigating the thalamus have done much toward complete analysis of the electrical activity within the central nervous system which will be described in discussing cortical organization.

F. Taste

Thalamic localization of taste has been observed by Ruch and associates (49, 50, 51) in monkeys and chimpanzees. The arcuate nuclei (nucleus ventralis posteromedialis) of the thalamus subserves taste, and hence taste and somatic sensation of the tongue are contiguously represented in the thalamus as they are upon the cortex. These conclusions were the result of experiments in which monkeys and chimpanzees were trained to discriminate taste. Horsley-Clarke lesions of the thalamus were then made and the effects upon the learned procedure examined. When the arcuate nucleus had been damaged the animals were unable to detect taste differences to the degree of their preoperative performance.

III. MOTOR SYSTEM

A. Medulla

Isolated functions of various motor nuclei of the medulla have been studied. One entire issue of a volume of the *Journal of Comparative Neurology* is devoted to the work of Crosby, Woodburne *et al.* (52) on the structure of the mammalian midbrain and isthmus region. It deals largely with the nuclear patterns of the cranial nerves.

The course, fiber composition, and visceral somatic, motor, and

sensory components of the facial nerve have been traced (53). Stimulation of the tegmentum above this area has been made to produce purposeful facial patterns indicating synkinesias between facial movement and the eyes and between face and respiration (54). The functional representation of oculomotor and trochlear nerves has been also determined (55). Focal centers for salivation in the medulla of the cat are reported by Wang (56). Stimulation of these points by the Horsley-Clarke technique results in copious salivary secretion.

Respiration.—This function has received a great deal of elucidation due largely to the work of Pitts which was begun earlier and has been reported in detail in previous volumes. It is now certain that sharply differentiated respiratory areas can be delineated in the medulla. Horsley-Clarke stimulation of the reticular substance of cats and monkeys by Beaton & Magoun (57, 58) confirm the existence of expiratory and inspiratory centers at the level of the inferior olive. The inspiratory field lies dorsal and medial, while the expiratory field lies peripheral to the inspiratory. Pitts correlates functional areas with morphological differences (59). In a summary of his previous work he divides the central respiratory system into four parts (60): (*a*) a respiratory central motor system; (*b*) a vagal inhibitory system; (*c*) a brain stem inhibitory system; and (*d*) other excitatory and inhibitory systems.

Part (*a*), even when isolated, functions rhythmically. Parts (*b*) and (*c*) function similarly to cause periodic inhibition of (*a*), thereby inducing rhythmic respiration. Phrenic motoneurones (61, 62) are played upon by discharges over spinal respiratory pathways in such a way that facilitation results from delayed pathways or reentry circuits within the center rather than from interneuronal spinal repetetive activity. The repetetive discharge of these motor neurones depends upon a balance between degree of excitation and rate of recovery of excitability.

B. Cerebellum

During the past three years the concept of the function of the cerebellum has been clarified so that for the first time clinical and experimental data can be correlated. It is all based upon earlier work of Larsell (63) who separated the cerebellum into three parts according to phylogeny and function: the archicerebellum, related to labyrinthine sense; the paleocerebellum, concerned with pos-

ture; and the neocerebellum, integrating volitional movements of the limbs in close association with the cerebral cortex. The subsequent work of Dow (64) on the posterior vermis and of Connor (65) on the anterior vermis have thoroughly confirmed the original postulates of Larsell. Bailey (66) has summarized these findings and applied them as they relate to man. Based on these concepts, Adrian (67) has confirmed the findings of Dow as to focal representation of spinocerebellar connections. In the rat, Dow & Anderson (68, 69) trace the distribution of the dorsal and ventral spinocerebellar tract into the anterior vermis, the paleocerebellum of Larsell, which is concerned with postural adjustments and tonus. It has been found that exteroceptive stimuli produced by moving a hair and proprioceptive produced by tendon tapping have different focal representation. In records from the cerebellar surface, the former type of impulse appeared chiefly on the culmen and the latter on the pyramis. The focal points were not, however, entirely discrete and no localization of body parts appeared.

Clarke's column has now been definitely implicated as the nuclear origin of the dorsal spinocerebellar tract. By following the electrical responses within this tract, Grundfest & Campbell (70) established its endings within the vermis. The tract is of large fibers and conducts at high velocity. The distribution is chiefly ipsilateral and to the culmen, but partly contralateral also.

Afferents from the cerebral cortex to the cerebellum have been traced via pons to mossy fibers by the Marchi technique; the lesions of the pons by means of which these fibers were traced were thought to induce ipsilateral hyperreflexia (71). Dow (72) has traced action potentials from cerebral cortex to the surface of the cerebellar hemispheres in cats and monkeys. The responses are most marked contralaterally and are recorded over the entire area of cerebellum receiving pontine fibers. In the monkey, areas 4 and 6 and the postcentral gyrus were the regions from which most widespread responses in the cerebellum could be obtained. There was a slight focal pattern representing face, arm, and leg within the cerebellum.

Smyth (73) traced, in man, the changes in cerebellum which result from tumors of the frontal region of cerebral cortex. Lesions involving areas 4 and 6 caused retrograde changes in the contralateral dentate nucleus. No such changes were found following parietal tumors. In this paper the relation of tremor to the frontal poles is discussed and the conclusion is reached that such tremor

although simulating the intention tremor of the cerebellum must be of cerebral origin. The same conclusion has been reached by experiments which produced action tremor following extirpations of area 6 in monkeys (74).

Following earlier experiments on animals, it has been shown that definite movement may be obtained by stimulation of the human cerebellum. This movement was described as bilateral and affected the lower extremities only in the three cases examined (75). Brogden & Gantt (76) have reported the conditioning of cerebellar reflexes.

In summary it may be pointed out that during the past three years our increasing knowledge of the cerebellum has produced a coherent and reasonable picture of its functions. Into this, anatomical, physiological, and clinical data are fitted. Fundamental for this concept is the division of the cerebellum into three parts which appear in both phylogenetic and embryologic development. The oldest part of the cerebellum lying in the posterior region of the vermis develops with the need of the animal for orientation in space. It is directly connected with the vestibular apparatus. Its removal in any form of animal results in disorders of equilibrium, and shows itself in vertebrates by difficulty in maintaining postural body adjustments. The second oldest part of the cerebellum lies largely in the anterior part of the vermis—a second part of it lies adjacent to the posterior vermis and is separated from the anterior division by a portion of the neocerebellum. This paleocerebellum is directly connected to the spinal cord by both afferent and efferent tracts. Its function is to integrate the postural adjustments which have to do with segmental cord reflexes. It develops with the development of the limbs. Injuries to this region result in reflex changes manifest in man by an increased supporting response and by tonic "cerebellar fits." In the four-footed animals there is also constant increase in extensor reflex tonus. The third part of the cerebellum, the neocerebellum, consists of all of the hemispheres and the midportion of the vermis. Its afferents are from pons and cerebral cortex. It develops with the cerebral cortex and hence is very much larger in man than in other animals. Its function is to smooth and integrate the phasic voluntary movements which are also integrated within the cerebral cortex. Lesions of this portion of the cerebellum cause the disorders of voluntary movement which are known as ataxia or intention tremor. Hypotonia also results.

C. Basal Ganglia

There has been much investigation of the caudate, putamen, and globus pallidus which, through 1941, is reviewed in a volume of the *Association for Research in Nervous and Mental Disease* (9). Since the basal ganglia are so closely involved in the extrapyramidal system some of their function will be discussed later with that of the cerebral cortex.

The connections between cerebral cortex and basal ganglia originally described by Cajal have been confirmed by Glees (77). Previously, in spite of good physiological evidence, many observers had been unable to discover any marked tracts passing from the extrapyramidal motor cortex to the basal ganglia to which they are functionally related. Glees, however, has found numerous nonmyelinated interconnections between the motor cortex and the caudate and putamen. The Ransons (78, 79, 80) describe the interconnections of the caudate, putamen, and globus pallidus and the course of efferent fibers leaving globus pallidus and passing via the ansa and fasciculus lenticularis to the subthalamic nucleus and, in very large numbers, to the hypothalamus. The connections with the cortex have been further differentiated by functional means (81), for the caudate has been found in monkeys to connect directly with the suppressor regions of the cortex, whereas areas 4 and 6 send fibers to putamen and to external part of globus pallidus. Rosegay (82) found no degeneration in the caudate, putamen, or globus pallidus of cats after massive lesions in the substantia nigra. Lesions of caudate head, however, produced degeneration, probably retrograde, in the substantia nigra. He found many nonmyelinated fibers within both sets of nuclei. His discussion of previous anatomical evidence is excellent.

Harman (83), measuring the total volume of the caudate and putamen of primates, finds that although the cortex as compared to basal ganglia increases as the primate scale is ascended, actually there is an increase in size of basal ganglia as well as cortex. The putamen, relative to the caudate, becomes much larger as the scale is ascended.

In animals, the effects of lesions placed in various basal gangliar nuclei have been recorded. Ranson & Berry (84) after making large lesions in the globus pallidus of three monkeys, state that they can find no physiological consequences thereof.

But Mettler (85, 86), making extensive ablations from various

parts of cortex and basal ganglia, has studied the resultant physiological changes as well as the ensuing degeneration. He concludes that there are differences between the motor behavior of monkeys from which only the cortex has been removed as compared to those from which the same amount of cortex together with basal ganglia has been extirpated. "Superposition of striatal ablation upon hemidecortication causes little specific further loss of motor capacity" but "there is much less 'spasticity,' as measured by resistance to passive movement, the assumption of specific postures, lowering of reflex threshold, increase in the force of reflexes, extension of the reflexogenous zone and spreading of reflexes, after hemidecortication alone than after removal of both cortex and caudate and/or putamen" (86). Removal of the striatum in addition to the cortex also limits the amount of movement and degree of variability although specific individual movements are still possible.

Kennard & Fulton (87, 88), following a series of experiments in which lesions were made within the various basal gangliar nuclei, singly or in conjunction with cortical lesions, support the evidence of Mettler that the motor cortex works in conjunction with the basal ganglia. Both tremor and rigidity were produced in monkeys and chimpanzees by large lesions confined to the caudate and putamen. The same effect could be produced by much smaller lesions of these nuclei if combined with ablations from the cortical area 6. The bilaterality of function and the nonspecificity of focal areas within the caudate and putamen are emphasized in these investigations. No focal regions were identified although the putamen seemed to be slightly more concerned with face and hand than was the caudate. The effects of basal ganglia ablation were always slight and transient in the monkeys, but more severe and longer lasting in the chimpanzees.

Because of interest in the abolition of athetosis and tremor by cortical extirpations, there have been many clinical observations of the effects of various lesions on such involuntary movements. These have been well summarized by Bucy (89, 90, 91). There seems now no doubt but that tremor or other involuntary movements can be abolished by removal of the cortical motor area focally connected with that tremor. Thus removal of the entire arm area 4 and 6 can abolish or greatly diminish involuntary movements, without the superimposition of too much paresis (91). That the operation can be carried out without producing some paresis

is doubtful. Attempts to abolish involuntary movement by severance of extrapyramidal pathways in the cord have been only moderately successful (92). And section of these pathways in the medulla, attempted in only a few instances (93), have been unsuccessful. By the last procedure impairment of pain and temperature control was also produced. Isolated reports on the abolition of Parkinsonian tremor by lesions producing hemiparesis in man confirm the above findings (94, 95). Hemichorea, or hemiballismus, likewise is still considered as due to alterations within the basal ganglia although the mechanisms thereof are not clearly understood (96).

In summary, it may be stated that the status of understanding of the role played by basal ganglia in motor performance has been altered and clarified by considerable anatomical, physiological, and clinical research. The postulate of Kinnier Wilson made 30 years ago (97) that the basal ganglia are intimately connected with the cerebral cortex and with its so-called extrapyramidal system in particular has been reinforced with experimental detail. The basal ganglia are now known to be concerned with spasticity or increased resistance to passive manipulation since this is heightened by their injury when the cerebral cortex has been damaged. The basal ganglia are also directly concerned with involuntary movements such as tremor, chorea, or athetosis. The production of such movements is caused by interference with that part of a corticosubcortical circuit which lies within the basal ganglia. Such movements have been diminished or obliterated by lesions placed outside the basal ganglia within the circuit—as in the cerebral motor cortex—or in the final effector tracts of the extrapyramidal system. It has been shown that there is no focal representation within the basal ganglia but that there is great bilaterality and nonspecificity of function therein. The effects of lesions limited to these nuclei are minimal in monkeys but are greater in chimpanzees and probably even more so in man. Both tremor and spasticity following basal ganglia lesions are augmented when the lesions are combined with cortical destruction of the extrapyramidal system.

D. Pyramidal System

The pyramidal tract has received some of the most exact and enlightening investigation of this period. It follows the lead of Marshall, of Tower, and of Fulton which will be found reviewed

elsewhere (1). Much of it will be dealt with in the section on cortical motor function.

Lassek has examined the fiber content and cells of origin of the pyramidal tract of ungulates (98), monkeys (99 to 103), and man (104, 105, 106) and presented, in addition to exact anatomic evidence, a number of physiological conclusions. The pyramidal tract, as it lies in the pyramids, ventral to the medulla, has been found to contain many times more axons than there are Betz cells in the cortex. In the monkey (99) there are about 18,000 Betz cells and about 554,000 axons. The fibers are mostly of small caliber, there are a fair number of medium sized fibers and only few of large size such as come from the Betz cells. It is pointed out by Lassek that the term Betz cell is, however, nonspecific being used merely to designate the exceedingly large cells found in area 4 of the cortex, which degenerate when the pyramidal tract is sectioned. There is no way of differentiating the smaller Betz cells from larger motor cells not usually called Betz cells. Lassek's emphasis on the small, slowly conducting fibers which comprise most of the pyramidal tract is in contradiction to the usual idea of a quick-conducting voluntary motor system mediated solely through the pyramidal tract (106).

Furthermore, it is now clear that the pyramidal tract contains a relatively small percentage of fibers deriving from area 4 of the cortex. Lassek (101) extirpated both the precentral gyrus (area 4) and the post-central areas in various monkeys and found degeneration of only a small per cent of fibers in the pyramids: if area 4 only was removed, the pyramid became roughly 13 per cent smaller on the affected side than on the normal and about 68 per cent of axons remained. If the postcentral gyrus was removed, about 86 per cent of axons remained after degeneration and the pyramid had shrunk to about 76 per cent that of the other side. If both pre- and postcentral regions were removed, still only 50 per cent of axons had disappeared. Peele (107) has reached the same conclusions after extensive examination of Marchi degeneration within pyramidal tracts following lesions limited to the postcentral gyrus. He concludes that area 3, areas 1 and 2 and, to less extent, area 5 project as far as the lumbar level of the cord of the opposite side. Area 7, however, sends fibers to the cervical region only, and area 3 sends a few ipsilateral fibers to the cervical region. In the opinion of Peele this parietospinal system offers a background for a sensitizing

fast-acting pathway whereby motor response to tactile sensibility may be brought about.

In addition to confirming the above anatomical findings, Welch & Kennard (108) report that although ablation of pre- or postcentral areas, or both, results in only moderate destruction of fibers within the pyramid, removal of areas 4 and 6 causes a somewhat greater degeneration and hemidecortication, in monkeys, is followed by a total disappearance of all fibers within the contralateral pyramid as shown by Weigert technique. No degeneration is found in pyramids when either the occipital pole or the frontal pole (areas 9 to 12) are removed. The origin of the fibers which make up the remaining bulk of the pyramidal tract after removal of areas 4, 6, and the postcentral gyrus, must thus lie in the remaining portions of the parietal and frontal lobes and possibly in parts of temporal lobe as well. This type of anatomical observation is borne out by investigations which record the physiological results of progressive removal of larger and larger bits of cortex in the monkey. A progressive increase in motor deficit occurs (86, 109) as will be described later.

The habit of describing a new form of plantar reflex associated with pyramidal tract disturbance and then, in most instances, of applying one's name to the "new reflex" has become intensified during the last few years. No attempt will be made to cite articles illustrating this obsession of individuals who often do not seem thoroughly acquainted with the literature on the subject. Wartenberg (110) has made an admirable attempt at clarifying the situation in what is apparently the first of a series of articles upon the reflex. In it the basic principle of the stretch reflex is described and the status of the deep reflex is simplified by applying to it the underlying principles which make significant a series of such reflexes over the surface of the body.

The same author (111) comments on the value of the various abdominal reflexes. The superficial skin reflexes, obtained from stroking the skin of the abdomen, are lost following pyramidal lesions but the deep reflexes, obtained by tapping the abdominal muscles or their insertion in the lower ribs, are heightened after pyramidal injury as are the knee jerks. Both skin and deep reflexes, however, are lost when spinal lesions at this level occur.

The spinal mechanism of the pyramidal tract has been further analyzed (112). A single stimulus applied to the pyramidal tract

at the level of the olive in cats, resulted in a series of impulses which were conducted throughout the length of the spinal cord. The activity of the pyramidal fibers could be recorded only from a very small area in the dorsolateral column of the cord. Then activation, synchronous at the medullary level, became altered into asynchronous activity of much longer duration within the pyramidal tract. The functional connections of this tract were then traced within the gray matter. Spinal reflex reinforcement of pyramidal activity began with the onset of movement. The motor system of the spinal animal was found to have tonic discharges.

In a series of articles describing the effects of chordotomy in man, Hyndman (113, 114) adds to our knowledge of reflex status in relation to the spinal cord. Section of the anterior half of the cord, affecting only extrapyramidal systems, results in no motor symptoms except transient weakness, especially in the extensor postural muscles. Mild injuries of the pyramidal tract with anterior columns intact cause acute hyperreflexia and spasticity of marked degree with exaggeration of extensor postural adjustment which, according to Hyndman, is due to release of extrapyramidal function. However, if the anterior columns are cut and only mild injury to the pyramids is sustained, there is no spasticity although hyperreflexia may be present. The spasticity which follows total section of the cord is of a different sort and, the author thinks, due to a different mechanism. It is chronic, appearing only late in the picture.

Confirmation of the loss of extensor tonus and the consequent flexor posture when the extrapyramidal tract alone is injured is obtained following ablation of the mesial portions of area 6 from the cortex. This is followed by a flexor paresis with hyperreflexia (74).

Discrete interruption of the lateral corticospinal tract in the cord is reported to result in paresis, which is flaccid (114, 115), and is accompanied by hypoactive reflexes indicating that no descending inhibitory pathway is present in the dorsolateral corticospinal tract of the monkey. The paresis is more pronounced in the lower than upper extremities and in the distal than in proximal muscle groups. These findings are in agreement with much previous work, namely that cortical injury affects distal rather than proximal joints, and that section of corticospinal tracts in the medulla causes hypotonicity. They are at variance with other findings—that fingers are usually affected more severely than toes following cortical

or internal capsule injury. They are probably to be explained by the arrangement of laminated fibers within the lateral corticospinal tract, which is such that the fibers to upper extremity lie deeper than those to lower. A sectional cut might then miss some fibers to the arm more easily than fibers to the leg. The explanation for the other variant fact, that section of this tract is followed by flaccid paresis, whereas the majority of cases of injury to lateral columns of the cord result in spasticity and hyperreflexia, lies probably in the fact that the rubrospinal tract is just ventral to the corticospinal tract and must in the latter case be injured with pyramidal fibers. Furthermore, although complete hemidecortication produces complete degeneration in the medullary pyramid, the dorsolateral area of the same cord still contains some normal axons (108) These then must be subcortical and extrapyramidal fibers, not present in the medulla but joining the tract at a lower level. They are, perhaps, fibers which when severed have a tendency toward influencing the cord to hyperreflexia.

This work of Hyndman on the cord as well as that of Mettler (116, 117) and Kennard (109) dealing with higher levels has shown that the fibers mediating extrapyramidal influence are widespread in origin and distribution and that the effect of extrapyramidal lesions is nonspecific and cumulative rather than focal as it is within the pyramidal system.

IV. CEREBRAL CORTEX

A. Motor Cortex

This subject has been well covered by Fulton through the year 1941 (1) and is the subject of a monograph to appear shortly (10).

To the anatomical data cited in the last section should be added the work of Conel (118) on the cortex of the one month human infant describing the development of the motor system and comparing it with the status at birth which he has described in an earlier monograph. It is remarkable to those who have not studied the histology of the infant central nervous system how undeveloped its cortex is. Not only its myelin structure but also its dendrites and synaptic connections are far from complete. The cortical cells appear round, smooth, undifferentiated, and devoid of Nissl substance as compared with those of the adult.

Pyramidal system.—The question of the cortical origin of the direct corticospinal tract is now solved beyond doubt. The work of

Lassek, cited above, confirms the earlier findings of many others that the Betz cells cannot be the sole origin of this tract, both because they are numerically many times fewer than the fibers and because the tract is primarily one of small fibers, some of them nonmedullated. It is therefore a tract conducting slow impulses for the most part.

The pyramidal tract remains the tract whose severance produces paresis of fine discrete voluntary movements. Such movements are largely distal and of the same type which can be caused by stimulation within area 4 of the motor cortex but not elsewhere. Flaccidity or absence of increase in resistance to passive movement is the undoubted result of selective injury to this tract. It has been shown (107, 108) that primary destruction of the postcentral gyrus in monkeys is followed by flaccidity, and (108) that primary removal of area 4 causes the same effect. It can be postulated that this is due to the fact that pyramidal influence and also Betz cells predominate in these regions as the source of corticosubcortical motor impulses, although extrapyramidal fibers are also present. If, however, these regions are removed together with extrapyramidal areas such as area 6, then the resultant paresis is spastic.

Extrapyramidal system.—The relation of the extrapyramidal system to spasticity has been confirmed by ablation experiments largely on monkeys (85, 88, 117) and the connection of this system to the basal ganglia has been emphasized by the same authors who found that additional removal of basal ganglia to motor areas increased spasticity.

In a review which offers no new evidence either experimental or clinical, Walshe (119) has come to the same conclusion regarding the anatomical indivisibility of the cerebral cortex into two systems. He agrees that, as has been known for many years, the pyramidal and extrapyramidal systems within the cortex are interwoven meshworks with areas 4 and the postcentral gyrus predominantly pyramidal in function and area 6 predominantly extrapyramidal. Thereafter he ignores all the evidence pointing to flaccidity as related to injury to the pyramids and as opposed to spasticity and insists violently that these two divisions can not be made. In a footnote of his text (5), however, having asserted previously that the extrapyramidal system is subcortical only, he notes the work of Tower & Marshall with regard to the effects of severance of corticospinal tracts and its resultant flaccidity. He

seems completely ignorant of the evidence regarding the strip area, 4s.

The question of "tonus" has been dealt with by Hoefer (120) who, continuing his previous investigations, records the potentials obtained from striated muscle in man under various conditions. Whereas there is no potential from resting normal muscle, the spastic muscle always maintains activity. The active fibers of such spastic muscle fire en bloc and not individually as do those of activated normal muscle. Resting spastic muscle, however, has no activity and activated spastic muscle maintains activity only in the muscles which are maintaining posture. Rigidity, of subcortical origin, is maintained by the constant activity of antagonistic muscle groups. Langworthy (121) reviewing the effects of cerebral injury in the cat, describes postural and reflex changes in detail.

Bilateral simultaneous ablation of the mesial portion of area 6 of monkeys resulted in a paresis in flexion with hyperreflexia as opposed to that in extension which follows removal of areas 4 and 6 bilaterally (74). A tremor of marked degree is present also.

Tremor.—The relation of tremor to the extrapyramidal system has been studied (74, 88). Bilateral lesions of area 6 will produce in monkeys a tremor which is absent during rest but present during postural tension or movement and is accentuated by emotional stress, by fatigue, or by the inception of voluntary movement. It differs from the intention tremor of the ataxic cerebellar animal in that it becomes less as motion is continued and not greater as does the true intention tremor. In monkeys it is transient and appears bilaterally following bilateral lesions, but is scarcely perceptible following a unilateral lesion. It is greatly increased both in amount and in duration when lesions of caudate or putamen are added to lesions of area 6. Removal of area 4 will temporarily abolish or diminish it as long as the resultant paresis of voluntary movement lasts. The therapeutic use of this has been discussed under the section on basal ganglia.

Epilepsy.—There is a large literature on convulsive attacks and epilepsy most of which will be dealt with in the chapter in this volume on brain potentials. The experiments of Kopeloff, Barrera & Kopeloff (122) who are able to induce periodic focal convulsive seizures in monkeys by the application of a substance to cortical motor areas are significant. Previous to their work no one had been able to produce recurrent attacks by a single previous procedure.

Payne, Clark, Ward & Cowden (123) record atypical seizures elicited from electrical stimulation of the cortex which were in character like those induced by direct stimulation of the cerebellum in the experimental animal. The propensity of the epileptic to seizures as the result of small stimuli is illustrated by the work of Williams (124) who caused petit mal attacks in epileptics by administration of cholinergic drugs. No such attacks could be induced by the same drugs in normal individuals. Convulsions in nonepileptic patients are reported on withdrawal of barbiturates, alcohol, and other drugs (125). The pathway of cortical impulses during induced epileptic seizures are recorded via pyramidal and extrapyramidal tracts. Section of the corpus callosum caused a rise in threshold and shortened seizures. Section of the pyramids altered but did not abolish the motor manifestations of cortical excitation (126).

Monkeys, particularly infant monkeys, were found to be very prone to postoperative epileptic seizures which might be severe and last many weeks, when the caudate and putamen were injured in addition to area 6 of the motor cortex (88, 109, 127). This observation fits with the well known clinical one that young infants, at a time when the cortex is neither myelinated nor functioning, are prone to convulsions following cerebral damage.

B. Sensory Cortex

Somatic sensation.—Understanding of the part played by the parietal lobe in sensory function has been increased by Marchi studies (107) and by use of functional anatomy, notably in the hands of Woolsey, Marshall & Bard (128, 129).

Peele describes the cytoarchitectonic areas of the parietal lobe of *Macaca mulatta* as similar to those given for another species by Brodmann. Interhemispheral connections are to adjacent cortical areas in the same hemisphere and to symmetrical, contralateral, parietal areas by way of the corpus callosum. All parietal areas send fibers to focal regions of the thalamus and some to pontine nuclei. The corticospinal direct connections of the parietal lobe have been described in a previous section.

Woolsey, Marshall & Bard, by the painstaking method of stimulation of one tactile organ such as a hair, and then recording the site of the evoked potential on the cortical surface, have mapped the sensory area for touch in the monkey and chimpanzee. The

representation is similar in the two species and lies so that below T1 there is a dermatomal projection upon the cortex. In the cervical region the same dermatomal arrangement exists but it is in reverse order, representation for T1 thus lying adjacent to C2 and C8 next to the face representation. In the opinion of the authors this accounts for the division of face, arm, and leg areas made by Dusser de Barenne and associates.

Adrian uses the same method for determining sensory areas of ungulates (130) and other mammals (131). His discussion of the teleological needs for the representation in various species is interesting. The rabbit has largest mouth parts; in the cat, the claws are largely represented, and in the dog, the face. The monkey has largest representation of both lips and hands. Marked variations in type of response under different anesthetics are recorded.

The phantom limb, always of necessity a dramatic source of interest to those studying pain, has become more common since the war and the sulfa drugs have produced many individuals who live after amputations. Both White (24) and Livingston (7) discuss theoretic and practical points on this subject. It has been shown in those individuals who not only feel that the amputated extremity is still present, but are disturbed by extreme pain in the area that the latter is due to injury to peripheral nerves. This pain is relieved at times by sympathectomy, but de Gutierrez-Mahoney (25) has abolished it by removal of the parietal sensory area representing the limb. Admitting that the painful phantom can be stopped by interrupting anywhere the chain of afferents leading to consciousness, he postulates that these afferent pathways have been found to be multiple and that it is therefore simpler to remove the region of the postcentral gyrus wherein pain is represented to consciousness.

Riddoch (132) compares the painful phantom limb with other disturbing paresthesias. Such pain may appear without amputation if the postural sense only has been destroyed. A similar pain appears following section of dorsal roots or cord injury. This resembles the so-called thalamic pain which, although represented in the thalamus, is not always due to lesions there. Parietal ablation will remove any such phantom pain.

Functions other than sensory have been attributed to the postcentral cortex and are in some way involved with the afferent impulses to that area. Flaccidity as a result of purely postcentral

lesions is described (107, 108) and growth asymmetry due to lesions of the postcentral cerebral cortex has been found by Penfield & Robertson (133). The latter is marked when the lesion is present in early childhood and is most extreme in face, arm, and leg. Lesions during the later growth period also produce changes, but of less magnitude. Such atrophy may also occur when only motor areas are damaged, but it is not marked unless the postcentral regions have been injured either alone or together with the precentral.

Auditory function.—The representation of hearing on the cortical surface has been surveyed by the meticulous investigations of Woolsey & Walzl (134) and of Ades (135, 136). By electrical stimulation of cochlear points after surgical exposure, Woolsey & Walzl were able to map its point-to-point projection. Primary pathways terminate in a laminated system and there is complete bilateral representation of one cochlea within a primary area. There is also a secondary auditory area lying ventral to the primary on the surface of the monkey's temporal lobe. This area is separate and has a higher threshold of excitability. Each area derives from a different part of the mesial geniculate nucleus. The same conclusion as to the extent of the primary area was reached by Ades & Felder (136), using click stimuli and recording from the exposed superior temporal gyrus. By strychninization of the primary auditory area impulses have been traced to the secondary acoustic region lying in the posterior temporal gyrus (135).

Galambos & Davis (137) studied the responses of a single auditory nerve fiber. The stimulus was a sound to the ear. Individual fibers were found to be sensitive to certain frequencies only. The fibers behaved in every respect like those of other sensory systems. Continued stimulation caused trains of impulses initially high, but soon declining gradually in rate. Rate adaptation was complete in a few tenths of a second. Pitch is a function of "where," and loudness a function of "how much" of the basilar membrane is stimulated.

Observations on auditory function whose implications are not clearly understood are furnished by the production of audiogenic seizures in the rat. Lindsley, Finger & Henry (138) produced such in susceptible animals noting the accompanying sympathetic and parasympathetic discharges, and postulated that the auditory center stimulates the hypothalamus. Beach & Weaver (139), how-

ever, find that hemidecortication will lower threshold and increase frequency of seizures and that total decortication causes even greater increase in the convulsions.

Olfaction.—There are scattered reports on olfactory function. Adrian (140) has traced the olfactory reactions in the brain of a hedgehog and finds that the normal cortical potentials, which are synchronous with respiration in this animal, are altered by smell stimuli. Lashley & Sperry (141) found that olfactory discrimination in rats was acute after destruction of the anterior thalamic nuclei which are supposed to be the areas of olfactory representation. Fox, McKinley & Magoun (142) present a long and accurate analysis of the oscillographic changes in cats. All the details of the olfactory system are traced. Indication of potentials transferred to the putamen and globus pallidus suggest a possible interaction between olfactory areas and striatum.

C. Associative Sensorimotor Areas

Building on previous clinical and physiological knowledge these three years have brought about considerable analysis of the complex associative motor and sensory functions which occur almost entirely in man. The background and present status of this subject are outlined by Cobb in two recent texts (11, 12). And the relation of such changes to alterations in "personality" are discussed.

The series of articles by Akelaitis and associates (143 to 148) is worth perusal by those interested in the subject of aphasia and related conditions. The primary objective of the authors was apparently to define the functions of the corpus callosum in mediating interhemispheral associations for these functions. It is remarkable that in this objective the findings were totally negative—there was no such function of the corpus callosum—yet the details of the study are so carefully reported (148) that it is of value.

Laterality, including handedness, footedness, and eyedness, was studied. The study of the higher visual functions in each homonymous field included absolute and relative orientation, absolute and relative discrimination of size and the recognition of color, objects and letters. Praxis was studied in detail. Auditory gnosis included the study of sound localization, the recognition of familiar sounds and the appreciation of music. Tactile gnosis included detailed study of the sensory system (tactile, pain, temperature, position, vibration, localization, deep pressure, two-point discrimination, weight discrimination, appreciation of shape, size, texture and consistency) and stereognosis. Temporal, spatial gnosis was studied. Language functions were studied unilaterally and included the receptive aspects, such as visual and tactile lexia, and the expressive aspects such as graphia.

Although associative functions linking the motor with the sensory are, for the most part, adjusted to a dominant hemisphere, neither destruction of corpus callosum nor of anterior commissure nor of both together influenced performance in any way. It was therefore concluded by the authors that other transhemisphere connections must be responsible for their effectiveness.

Lashley (149) offers evidence of a similar nature when he studies maze performance of rats before and after incisions separating adjacent pairs of cortical fields. Normal performance follows such operations.

Interesting analyses of individual cases of agnosia or apraxia have been reported by others with emphasis on the physiological interpretation and its interrelations with the Gestalt concept (150 to 153). In a discussion of anosognosia and autotopagnosia Olsen & Ruby (154) localize the origins of these somewhat unusual conditions. Anosognosia, imperception of hemiplegia, follows lesions within the right thalamus and internal capsule which cause hemiplegia and heminaesthesia; lesions of the right thalamoparietal peduncle which cause hemiplegia and amnesia for the paralyzed side; or lesions of motor and parietal cortex combined. The thalamus with its direct cortical connections thus becomes implicated in the hemispheral dominance.

Brain (151) discusses visual disorientation as a symptom of parietal lesions. Unilateral lesions result in homonymous unilateral disorientation. Spatial learned concepts are lost because the concept of the relation of the body to space is normally adjusted almost entirely through vision.

D. Frontal Association Areas and Temporal Lobe

There are a number of functions now assigned to these cortical areas bordering on the true sensorimotor cortex which may be closely associated with the simpler ones integrated through the motor and sensory areas. Other parts of the functions of these areas will be discussed in another chapter.

Temporal lobe.—The temporal lobes have been shown by Bailey *et al.* (155) to have numerous functional connections. Those of the acoustic areas in the occipital part have been described above. Less is known of the more frontal section. Area 21 of this region connects with the opposite hemisphere through the anterior commissure. Fox & Schmitz (156) cut the anterior commissure and

traced fiber degeneration thence into the olfactory bulb and other parts of the olfactory apparatus as well as into the temporal lobes. It is probably functionally significant that this association area receives large bundles of fibers from the frontal association areas in monkeys and chimpanzees (157) and that it is closely connected anatomically with both the olfactory apparatus and the hypothalamus. It is the only cortical area not receiving thalamic projections.

Bucy (158) has summarized his work and that of Klüver on the effects of ablation of the temporal lobes from monkeys. Behavioral changes are noted. The animals become less fearful and exhibit excessive curiosity. Gnostic sense is disturbed. The relation of these affective disorders to olfaction is not clear at the moment. Teitelbaum (152) discusses the principle underlying such behavioral changes following temporal lobe lesions in man.

Frontal poles.—It is probably significant also that the frontal association areas of the monkey and chimpanzee are composed of a number of small functionally distinct areas which have many connections with surrounding areas (157), and that there are connections with the motor cortex and temporal lobe.

Within the frontal association areas there is as yet no localization of any specific function with the exception of hyperactivity. This has been found to occur in many animals following bilateral frontal ablation (159) and is shown by Ruch & Shenkin (160) to appear in its entirety when only area 13, a small region on the orbital surface of the frontal poles, has been bilaterally ablated. This permanent increase in activity is unaccompanied in the monkey by any change in appetite, basal metabolism, or gastrointestinal function. It is unaffected by placing the animal in a soundproof room, but all hyperactivity is abolished in the dark (159). The perseverative, repetitive, and purposeless character of the movement is emphasized.

From the functional studies of McCulloch and his associates and from knowledge of corticoautonomic function it is clear, however, that although there may be no specific focal points in the frontal region it is divided roughly into three parts; that lying rostral to areas 6 and 8 which integrates complex learned motor acts related to these areas; that on the orbital surface which has largely to do with autonomic vagus function; and the tips of the frontal poles which are in some way related to affective behavior and to personality in man.

Two clinical procedures, frontal lobotomy and the use of shock therapy, have furnished experimental data on this last point. No attempts can be made here to cover the extensive literature on either subject. The review of Freeman & Watts in this volume last year (1944) discusses the physiological consequences of lobotomy.

Langworthy (121) gives an excellent description of the restlessness and distractability found after bilateral frontal lobectomy in the cat which is very similar to the condition described following frontal lobotomy or shock therapy in man. In addition to being hyperactive these cats are dirty and awkward in their motor activity. They show over-response to food, to stimuli, to other cats, and to usual cage situations.

Some key to the processes which bring about such changes is furnished by the work on conditioned reflexes, largely from the laboratories of Gantt (161) and Liddell (162, 163), and has developed from the study of experimental neuroses (164). Convulsions induced by metrazol (165), insulin, or electricity (166, 167) effectively destroy complex conditioned reflexes previously learned by experimental animals. Animals whose trained reactions have been inhibited or suppressed by lack of reinforcement do not normally regain the original trained habit without retraining. Following convulsions, however, the superimposed inhibition is destroyed and the animal returns to its previous conditioned activity.

Neuroses are induced in animals when experimental conditions become unsolvable as in the dog of Pavlov, trained to discriminate between a circle and an oval, which developed neurotic symptoms as the shape of the oval was gradually altered to approach that of the circle. To quote Liddell, the symptoms are the result of the superposition of innumerable shells of inhibitions and frustrations around the individual during growth and existence. Their removal, by induced shock therapy, thereby changes the conditioned concepts of the individual. Wikler & Masserman (168) record the effects of morphine on learned adaptive behavior in the cat as similar. Late learned responses are abolished first. Neuroses caused by conflict between hunger and fear were abated under partial morphine narcosis. It is now certain both clinically and in experimental neuroses that the affective states of anxiety and their accompanying autonomic manifestations can be dissipated by these means.

Following the original observations of Jacobsen that monkeys after bilateral extirpations of the frontal poles lost the capacity

for immediate memory, Malmo (169) showed that, in the same delayed response test used by Jacobsen, immediate memory was adequate when the tests were carried out in dim or nearly absent light. Morgan *et al.* (170), using rats, found that frontal lobectomy destroyed the capacity to solve delayed response problems as it had in Jacobsen's monkeys. This is not true, however, of any tests except those involving symbolic processes, for rats without frontal lobes are capable of learning or retaining the ability to solve any form of maze.

Harlow and associates (171 to 174) have tried all sorts of complex tests under the above conditions. Their final conclusion was that monkeys without frontal poles are able to solve any complex problems not involving symbolic concepts but that in these last their performance is far below that of the normal. Their absence of drive in cage situations and slowness in initiating acts, together with larger fractions of error in learning, are stressed rather than the absence of any specific quality related to memory or learning.

Lashley (175) has contributed to our knowledge of the functions of the occipital lobes of rats. These animals may learn to solve a maze and then, following removal of the eyes, relearn the maze with relative ease. Removal of other parts of the cortex does not alter this capacity, but removal of the primary visual cortex produces great loss of ability to relearn. The deterioration of the habit following occipital lobectomy is ten times that following enucleation of the eyes. Animals which have had enucleations and then been taught maze solution have the same difficulty in relearning if the occipital cortex is removed at a second operation. Lashley therefore suggests that in the rat there is, in the primary visual cortex, a nonsensory element which is specific to that area. It is of the order of the functions found in frontal poles and may belong to the associative areas of the visual cortex.

V. CORTICAL ORGANIZATION

A. Electrical Properties

Continuing their work in physiological neuronography McCulloch, Bailey, Garol, and associates have finally traced the interconnections between all cortical fields in monkeys and chimpanzees. When the mesial aspect of the cortex of monkeys and chimpanzees was mapped, a suppressor band was found which connected with each of the suppressor areas on the lateral surface (176). The in-

terrelations of the frontal pole areas were obtained and here area 8 was found to extend from the lateral surface over onto the midline regions of the orbital surface, thereby forming a suppressor band completely dividing the motor areas from those of frontal association region (157). The long association fibers of the primate cortex have been traced. Determined electrically following strychninization, the long tracts of the chimpanzee are found to be homologous with those traced anatomically in the brain of man (177). The functional interhemispheral connections of both monkey and chimpanzee are also similar to those traced anatomically. No fibers passed from suppressor areas across the corpus callosum although there is always bilateral activation of these areas. Areas 9, 5, and 6 send largest numbers of fibers into corpus callosum and chiefly to their homologous region on the other side. The anterior commissure carries fibers from area 21, the rostral portion of the temporal lobe (178, 179). It has been demonstrated that a suppressor area is present in man by stimulation of the cortex rostral to the motor area in a region homologous to that of area 4s in the monkey and chimpanzee (180).

Rosenblueth & Cannon (181) have reviewed most of the previous work on the characteristics of cortical excitability. In addition to confirming much of this they add some new observations, probably the result of the use of chloralose rather than barbiturates as anesthetic. They postulate for the cortex two types of motor response to thyrotron stimulation, a direct tonic-clonic response to stimulus and an indirect "self-sustained" response induced by higher stimuli. This self-sustained response appears after direct stimulation of area 4 but may be produced from other parts of the sensorimotor cortex. They demonstrate effectively that the result is not due to spread of current but rather to spread of excitation. No such self-sustained responses can be produced from either thalamus, striatum, or cerebellum and the conclusion is that such responses are specific to the cerebral cortex. The properties of facilitation and inhibition are investigated and conclusions reached which confirm those of earlier experiments. The relation of the self-sustained activity to electrocorticogram is discussed.

Tracing cortico-subcortical connections in the chimpanzee, Garol & McCulloch substantiate previous findings in the monkey that the suppressor areas connect with caudate nucleus while areas 6 and 4 send fibers to putamen and to globus pallidus (182). The

effect of acute subcortical lesions on electrocorticograms has been studied. Definite characteristic potential changes of rhythmic quality have been obtained from striatum and thalamus of decorticate monkeys (183). These potentials may be recorded from the subcortical nuclei while the cortex is intact, but are modified to resemble cortical potentials unless all of the cortex has been removed. Destruction of the hypothalamus following decortication abolishes these potentials. In monkeys, chronic lesions of basal ganglia and thalamus altered EEG in characteristic manner; lesions of hypothalamus in monkeys (127) and cats (184) diminished or abolished such activity.

Stimulating the thalamus, Morison & Dempsey (44, 45, 46) have traced and recorded electrocorticograms from various parts of the cerebral cortex and describe a thalamocortical relay system (47). Following a primary response to stimulation of the mesial lemniscus-internal capsule relay system a repetitive sensory response appears which, as recorded from cortex, is similar to its spontaneous electrical activity. A mechanism for thalamocortical augmentation and repetition is described (48). Decortication reduces but does not abolish this type of response. Removal of thalamus prevents it altogether. Focal connection between thalamus and the portions of the cortex known to be anatomically connected were traced as were connections between brachium conjunctivum and motor areas (44, 45, 46). Two types of response, one focal, the other generalized, necessitate two different systems between cortex and thalamus one of which is nonspecific and has diffuse connections. The similarity in nature of recruited potentials following stimulation of the thalamus to spontaneous 5 to 10 per second activity of cortex is discussed (185). There are many characteristics in common. The recruited potentials can be made to wax and wane by recruitment and "decruitment" in a fashion similar to that seen in spontaneous activity. Characteristic spontaneous activity from subcortical areas is also recorded (45).

Walker *et al.* have modified cortical potentials by "driving" the cortex (186, 187, 188). Intermittent photic stimuli produce this driving effect on cortex altering the potentials recorded therefrom. Amplitude of response was increased under such circumstances, potential changes became more stabilized and regular. A fusion mechanism for the cortex was indicated which would limit the temporal resolving power of the primate visual system. Increasing

intensity of light from 4 footcandles to 80 footcandles doubled the effectiveness in driving the cortex. Monochromatic light was found effective, blue light being more so than was red.

B. Effects of Gross Ablation

Something of the organization of the cortex and its relation to subcortical structures has become known through a series of reports on the effects of decortication or of large ablations. Woolsey (189) records the progress of a monkey completely decorticated for 161 days. Langworthy (121) reviews the effect of decortication on cats in some detail. Mettler, using monkeys, made successive ablations of: frontal pole, frontal areas with 4s, frontal lobe, and entire cortex of one side, adding, in other animals, the striatum, all tissue to the posterior commissure, or both. His conclusions are that progressively more extensive unilateral ablations from cortex produce progressively more intense degradation in motor performance rather than abrupt paralysis. At the level of posterior commissure there is sudden loss of all but the simplest movements. Increased resistance to passive manipulation is increased when caudate and putamen are added to cortex (86, 88). But not until the thalamocortical circuit is disrupted is discriminating movement of the small musculature abolished.

C. Phylogenetic Organization

Von Bonin (190) by encephalometry has distinguished relative differences in the primate brain which are useful in the understanding of cortical mechanisms. According to his data, the relative changes in behavior of monkey and of man are dependent more on differences in intracortical organization than on size of cerebral hemispheres. In the course of evolution von Bonin finds that the primate brain becomes higher but not wider, and that the frontal lobe becomes relatively larger in man than in the macaque but that there is no significant difference between the chimpanzee and man. Parietal and temporal lobes increase more significantly, but the forms of all three primates, in all lobes, cling to a common pattern.

Internal structural differences are marked. Localization of function is much more possible in man than in the monkey. Cell size is greater in man. The significance of the temporal lobe is speculated upon. It is the only part of cortex not connected directly to the thalamus.

D. Growth and Reorganization

Such studies as that of Hines (191) add to our knowledge of the organization of somatic motor function. She notes the appearance and regression of reflexes, postures, and methods of progression in the infant macaque. The order of development of motor behavior and of response to sensory stimuli is correlated with the differential maturation of the nervous system exactly as it has been for the human infant by such studies as those of Gesell & Amatruda (192). In the infant monkey movement of the upper extremities was produced by stimuli of higher intensity than are required for the adult. The motor responses of the infant are less discrete than those of the adult. They did not occur in the lower extremities (193).

The capacity for reorganization of the cortex in respect to recovery of motor function following removal of part or all of the motor area of monkeys has been demonstrated (194, 195). Removal of equivalent cortical areas produces far less ultimate motor deficit in the infant than in the adult and subsequent removal of what are usually thought to be nonmotor areas from such infants shows that these latter have, in the absence of the true motor areas, integrated some part of the cortical motor function not usually represented therein. However, stimulation of the cortex of monkeys from which the motor areas 4 and 6 had been removed in infancy did not reveal any greater excitability or focal properties in remaining tissue than that which existed in adults following recovery from the same ablations. Cholinergic drugs were reported to facilitate recovery of motor function following lesions of the cortex (196).

Finally, in an admirable presentation of the work from the Laboratory of Dusser de Barenne and others, McCulloch (197) has reviewed recent knowledge of the functional organization of the cerebral cortex and has succeeded, in addition, in forming from the facts at hand an excellent working concept of the neuronal interconnections of the cerebral cortex as a whole and of its detailed intercortical and subcortical relations.

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THE SPECIAL SENSES

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The war has shown its influence on physiological literature pertaining to the special senses available from September 1943 to September 1944 in the appearance of an unusually large proportion of papers on three topics, night vision, color vision, and blast injury to hearing. It is, of course, inevitable that applied rather than "pure" physiology should occupy investigators at this time, and that there should be a dearth of material on many interesting problems in sensory physiology which appear to have no immediate practical application.

The Eye

Vision.—The records of nearly 200,000 American inductees show that more than 10,000 of them had uncorrectable impaired vision. Two-thirds of these defects were of traumatic origin and early care might have been effective in preventing amblyopia in the majority (1). In another much larger series of records it was found that there was between 0.5 and 3 per cent of ocular malingering (2, 3). Tests, however, have been improved and can, to save time, even be given in groups (4). The importance of vision in aviation and the effects of anoxia have been particularly emphasized, and it has again been pointed out that blue should be condemned for blackouts, since from great distances the dark adapted eye sees blue well; while white requires ten times the brightness of blue to be perceived and red one thousand times (5). At high altitudes also there is a definite effect on the relation between stimulus, intensity, and the latency of after-images. At 15,000 feet the light has to be 2.5 times normal intensity to be seen, and the latent period of after-images is greatly prolonged. The same general effect of anoxia has been observed for visual acuity and intensity discrimination (6).

There have been at least two reviews on the eye as an image-forming mechanism (7, 8). Re-examination of visual acuity at low brightness levels (9) and of peripheral visual acuity (10, 11) have been made. In the latter case the Landholt broken circle was used as test object and it was shown that although peripheral visual

acuity is widely variable in different subjects, it is best when the test image falls on the outer part of the extra-foveal area, least when it falls on the lower part. The lens, which is largely responsible for central acuity, is said to function hardly at all beyond 30 degrees from the line of vision. This work, however, has been criticized (12) on the ground that the Landholt broken circle cannot be used in examination of peripheral vision. The spectral sensitivity of the fovea and extra-fovea has been studied in the Purkinje range by finding the energy required at various wave lengths to match the brightness of a fixed comparison field (13). Surprisingly high intensities were required before the photopic curve was reached, which suggests that the rods may continue to function over a greater range of intensity than has been generally accepted. In the extra-foveal regions children have the ability to detect shorter wave lengths than older persons (14). Mathemetical formulae have been derived for changing visual curves for cone vision with the natural pupil to those which would obtain with a 2 mm. artificial pupil and the reverse (15). These calculations are of significance since the older conception that the effect of reducing pupil size could be exactly compensated by an increase in the helios of the test field does not hold. The rays entering near the edge of the pupil are much less effective than rays entering near the center of the pupil (Stiles-Crawford effect).

Flicker fusion tests have been tried out as a possible measure of fatigue without success (16, 17). Administration of large amounts of vitamins of the B-group seems to have no effect on the changes in critical fusion frequency due to anoxia (18). The test does, however, hold promise for recognition of certain neurological lesions (19), and has been used successfully in conditioning experiments (20). Crozier continues his use of flicker in his examination of visual mechanisms, having tested its relation within the fovea of man (21, 22, 23), with special reference to the duplicity theory (24), and with reference to the function of the pecten in birds (25). The latter appears to increase the sensory effect of small moving images. Crozier emphasizes the point that in visual duplicity we are dealing with two groups of neural effects, and that this does not necessarily mean differences in the fundamental excitabilities of the histological elements, rods and cones. Granit, in spite of the difficult times, has been able to continue his studies on electrical responses of the eye (26). He finds that in the case of isolated elements of the guinea pig's eye (a pure rod retina) the ma-

jority discharge at onset of illumination, whereas in the cat (a mixed retina) the majority of elements respond both at on and off. Pure on-elements number 20 per cent; there are few pure off-elements. His results lead him to propose a modified duplicity theory with the hypothesis that there are transition forms between rods and cones, and that synaptic organization is different in the two main types of elements—simpler for rods so that receptor effects are transmitted with less modification.

An excellent detailed review with extensive bibliography of the subject of dark adaptation in all its aspects, physical, physiological, clinical, and aeromedical, has been written by Sheard (27)—a valuable contribution to the literature. Army tests for night vision have become routine, particularly for fliers, and in the Canadian forces 7 per cent were found superior, 35 per cent good, 49 per cent fair, and 9 per cent poor in this respect (28). In the British army (29) an attempt has been made to obtain records both on the subject's minimum light sense and minimum form sense after 30 min. of dark adaptation—3 min. dark adaptation has little significance—since it is thought that together these two functions give a better measure of a subject's ability to see in the dark than the light sense alone. The Russians (30) believe they can increase night vision 30 to 50 per cent by a single application of some extraneous stimulus such as washing the face with cold water, or, best of all, mild physical exertion. Not only is the ability to see in the dark increased by these means, but the dark adaptation process is shortened from 30 min. to 5 or 6. This is explained by the enhancement of sensory effects through autonomic reflexes set off by stimulation of other sense organs, a mechanism suggested by Orbeli several years ago. Rod scotomas can be demonstrated by self luminous test objects and a red fixation light (31). About 20 per cent of normal subjects show a triangular scotoma starting about 20 degrees out from the fixation point. This represents the remnant of the secondary optic vesicle in the embryo. A ring of high rod sensitivity lies about the macula corresponding well to histological findings in the retina. Anoxemia in the low pressure chamber causes contraction of the field and enlargement of macular scotoma and blind spot, a state resembling early stages of vitamin A deficiency. The night blindness of war, however, does not yield to vitamin A therapy; therefore, although dark adaptation tests do measure the ability to see at low intensities, there must be a difference in the mechanisms of true night blindness and poor dark adaptation with reference to

vitamin A (32). Standard curves for dark adaptation form the subject of one of the few papers in German to come to hand (33), and in it the emphasis is on the unreliability of single estimations; tests must be carried out many times to obtain the true form of the curve for a given individual.

Retinene has been prepared *in vitro* in a state approaching purity (34). The term retinene is considered a misnomer and "retinaldehyde" is suggested. The subject of breakdown products of visual purple has been reviewed by Morton (35) and Krause (36). The differences between "indicator yellow" and "visual yellow" or "retinene" are emphasized and the suggestion made that the visual process involves more than splitting off of visual yellow from a protein, that the formation of indicator yellow is of importance, and that vitamin A affects photopic as well as scotopic vision. Evidence, corroboration of earlier work (37), that young persons have sufficient stores of vitamin A is given in a paper on Swiss children (38). During the late winter and early spring a group of Lausanne school children were given additional vitamin A without any change occurring in their adaptation curves. Another survey (39) shows that there is progressive deterioration in power of dark adaptation with increasing age, which, however, can be explained quantitatively by the progressive decrease in pupil size with advancing years. The Stiles-Crawford effect can be overcome by using fairly intense field brightness, in which case the visible effect of threshold brightness is directly proportional to the area of the pupil. The effectiveness of red goggles to reduce the time necessary for dark adaptation may be explained by the reduced brightness of the visual field, not by the particular wave length used, since a comparable effect is obtained with neutral filters (40).

The Committee on Colorimetry has given us precise definitions of light—"Light is the aspect of radiant energy of which a human observer is aware through the visual sensations which arise from the stimulation of the retina of the eye"; of color—"Color consists of the characteristics of light other than spatial and temporal unhomogeneties"; and a complete discussion of the physical, physiological, and psychical aspects of color (41, 42). There have been popular accounts of color vision (43), and relatively simple summaries of the subject of a more scientific nature (44 to 47). The question of tests is still hotly debated; there are those who contend that the Ishihara test is "unsatisfactory as a scientific instrument"

(48); others say that certain subjects classified as "color-blind" by this test should be designated "color-weak" (49); others find this test acceptable (50 to 53); while still others seem to prefer their own tests (54, 55). The classification of the color-blind more generally in use is (*a*) trichromats, subdivided into normal and anomalous, whose color vision functions on three variables; (*b*) dichromats, subdivided into protanopes (red-blind), deuteranopes (green-blind), and tritanopes (blue-blind), in all of whom color vision functions on two variables; and (*c*) monochromats, having one variable only. Protanopia and deuteranopia are usually physiological disturbances unaccompanied by pathological findings, whereas tritanopia is associated with disease, particularly detachment of the retina (46). Formulae have been derived to show the percentage of blue and red required by dichromats to match colors either on the basis of energy or brightness (56). Dunlap's claims of improvement in color vision by ingestion of large amounts of vitamin A have again been assailed (57), but other investigators claim that a diet of carrots will even improve nearsightedness "making more objects recognizable at a given distance and enabling the eyes to function more clearly at a distance" (58). Dunlap himself does not claim that all color-blindness is due to a single condition as diet, since vitamin A administration does not help color-blindness resulting from long periods of inhalation of wood alcohol as in those workers who prepare varnishes (59). Another treatment for color-blindness in men rejected from military service, the "Light and Filter" treatment, where the subject practices fixation of colored sources of light, is also condemned as time-consuming and affording no true improvement (60); and the explanation offered for the now notorious case of Aldous Huxley is that the subject learned how to use the visual equipment he had, rather than improved the equipment itself by exercise. Neurasthenic patients show distinct differences from the normal in the size and arrangement of their color fields, and such a list is of distinct value since it cannot be faked (61). Survey of color tests applied to the British navy suggests that color defect may be associated with race, since it is less prevalent in the north and east of Great Britain where light hair and eyes are prevalent, and more so in the south and west where dark coloring is the more prevalent (62), but a similar survey of Glasgow University students, however, does not bear out this conclusion (63). Records show that women with color-blind relatives are not so free from color weakness as formerly supposed; there is greater

incidence of red-green weakness than in women in general (64).

A significant contribution to the theory of color vision has been made by Göthlin of Upsala (65 to 69). The essence of his theory is that certain stimuli which give rise to one colored sensation can inhibit impulses which would give rise to sensation of another color. This assumption is justified by Granit's work on the electrical responses of the cat's eye where there is found a negative component of inhibitory character. The three fundamental colors would be red, green, blue—Göthlin gives experimental evidence that violet is not the third primary (68). Every impulse from retinal receptors giving rise to a color sensation is thought to be combined with central inhibition of the complementary color in the same area. Colored negative after-images would be due to the hyperexcitability of organs previously inhibited. The scheme may be likened to a sort of double balance, one arm of which is the single color, blue, the other a secondary balance of red and green. When red and green are themselves in equilibrium, yellow results; when red, green, and blue are in equilibrium, white results. When the red or green side of the small scale is preponderant yellow is inhibited, and a sensation of red or green results depending on which of the two is predominant. Protanopia and deuteranopia would be defects of the secondary balance, tritanopia of the main balance.

Another color theory (70), more difficult to understand, proposes that "colors arise as gradient phenomena taken with respect to adaptation level," a theory which the reader will have to study out for himself. Still another theory of color vision has been proposed (71) which postulates that both rods and cones are concerned with color, the rods in this case being of a special nature in that they do not accumulate visual purple or become dark adapted (72). This theory has been criticized on the theoretical ground that it demands two variables whereas the color manifold of the normal trichromat is clearly three dimensional (73), and on the practical ground that it does not fit certain experimental data (74).

Finally dissatisfaction has been expressed with all existing color theories on the ground that they all show inconsistency when they attempt to relate color-blindness to normal vision (75). This is based on comparing spectral saturation in the different groups, e.g., it is found that blue-green for the normal is highly saturated, less so for anomalous trichromats, and completely desaturated for dichromats. This is not consistent with theories which assume that in trichromats there are three kinds of cones yielding sensa-

tions of equal saturation, or theories which assume that the two types of cones in the dichromat have identical ranges of spectral sensitivity.

Hartridge (76) has made a study of the visibility patterns of blue and yellow. At sufficient distance blue becomes black, and yellow white. The phenomenon is explained by chromatic aberration of the eye which prevents simultaneous focusing of yellow and blue, a difficulty which he has made the subject of further study, showing that two factors must be taken into consideration: (*a*) chromatic aberration operating at small pupil apertures; (*b*) the Stiles-Crawford effect operating at large apertures (77).

Cornea.—The necessity for a knowledge of the physiology of the cornea has been emphasized by the recent use of transplanted corneas and Cogan (78) has continued his work on this subject. He finds that purely water-soluble substances do not pass through the corneal epithelium, while purely fat-soluble substances do not pass through the stroma. With the exception of water, substances which do pass through the whole cornea have characteristically biphasic solubilities and there is some transfer in either direction. The conjunctiva has properties of permeability qualitatively similar to those of the cornea, and the sclera to those of the corneal stroma. Corneal epithelium has a high oxygen uptake in contrast to low uptake by the stroma. The oxygen uptake is lessened in corneas of riboflavin-deficient rats. The metabolic activity of the xerotic cornea is normal or higher than normal, which may be accounted for by metaplasia and hyperplasia rather than actual cellular destruction (79). The corneal epithelium is the only important barrier to burns by acids or bases, and its protective effect has been calculated at different pH's (80).

Lens.—A very useful classification of experimental cataracts in the rat, complete with references, has been compiled by Buschke (81, 82). His articles include a description of his own work on tryptophane deficiency. The old question of dinitrophenol cataracts has been revived by Robbins (83) who finds that, even if other animals are not susceptible to this drug, chicks are. Opacities develop within five hours and persist as long as the drug is given. Since aviation medicine has inspired investigation of anoxia on practically every known physiological function it is not surprising to learn that cataract production has been investigated in rats and rabbits at reduced atmospheric pressure, and at normal pressures with low oxygen tension. Since after decompression the lactic acid

content of the aqueous humor is three to four times higher than normal, it is thought that the resulting cataract is occasioned by osmotic upset. Such cataracts last less than an hour, then regress. No opacities in the lens due to anoxemia were seen in human lenses under similar conditions (84). Use of an ophthalmic ergograph is found to fatigue accommodation ability in both eyes, even when one eye may be occluded. The fatigue is greater in the worked eye (85). To complete the record on the lens reference is made to the present author's recent summary of his work on the role of the autonomic system in accommodation (86).

Iris.—The most provocative recent work on the iris comes from Langworthy (87, 88). He has reviewed the evidence for the existence of dilator fibers in this organ and comes to the conclusion that there are none, or at least that they are unimportant for pupillary movement. The mechanism of dilatation is to be explained by changes in the blood content of the erectile tissue of the iris. Vasodilation gives a small pupil, vasoconstriction a large one. The role of the sympathetic is merely to provide a general tonic background; the parasympathetic is the nerve chiefly concerned. The argument leans heavily on the evidence that in certain animals, particularly the cat, reflex pupil dilation appears to be accomplished by pure inhibition of oculomotor tone, the afferent pathway for which has recently been worked out by Harris *et al.* (89). Langworthy's work may throw light on the pupillary reflex to darkness described by Lowenstein (90, 91) and its modification in patients, which has led him to postulate that there are separate pathways for the reflex movements of the pupil to light and to darkness. Incidentally, the histology of the iris has recently been reviewed in connection with experiments which demonstrate the inability of the iris to regenerate after surgical removal (92). Moving pictures show that the size of the pupil of the cat's eye is a function of the brightness of the stimulus as it is in man's, the variation being from 12.5 mm. in the dark to 1 mm. at 1,000 millilamberts (93).

Aqueous humor.—The question of the secretion vs. the diffusion theory of aqueous humor production is still being debated. Kinsey & Grant (94) hold from their work on heavy water that electrolytes enter the anterior chamber as a result of secretion, nonelectrolytes by diffusion. Duke-Elder (95) claims that the second law of thermodynamics demands that the whole process be one of secretion, since equilibrium can only be obtained if work is continually performed. Visscher (96) has used radiosodium in an attempt to settle the controversy, but is forced to admit merely that from all the

evidence available "passive" processes appear to be inadequate.

Lower animals.—Investigations on the eyes of lower vertebrates and insects have been few during the war. Retinal pigment movements in the frog appear to be better observed when the eye is transferred to the belly cavity of the animal than in artificial media, where for the first time elongation of cone myoids was observed. The most striking difference from the normal was the failure of the cells in this position to expand to heat (97). B-hormone from the intermediary lobe of the pituitary causes the retinal pigment of the frog's eye to assume the dark position more rapidly than in the normal eye (98). The lens in the salamander arises from ectoderm by induction of the eye-forming center. The action is strong before closure of the neural folds, weak later (99). In *Triturus* the lens can regenerate from the iris provided there is no lens present; the presence of a lens inhibits regeneration of another one (100). Frozen eyes transplanted into the adult salamander have little chance of recovery of function, but eyes transplanted after being chilled at eight degrees for two days recovered function within three months (101). Sperry (102) has observed the same phenomenon in *Anurans* that he observed in *Triturus*, viz. return of visual perception after optic nerve regeneration, with orientation of the animal in response to visual stimuli depending on the orientation of the retina. In the insect's lateral ocelli there are found two lenses, one external or corneal, the other internal or crystalline. Real inverted images are focused on the retinal elements. The rhabdom, because of its shape, is inadequate for the reception of images (103). The electrical responses of the dark adapted grasshopper eye show for brief illuminations a negative b-wave; for a longer period of illumination a slowly changing negative c-wave appears which is followed on cessation of the stimulus by a rapid negative d-wave, and a long after-potential, usually positive. To explain these different waves the theory is advanced that the electrical response is the algebraic summation of two components, one positive, one negative, and that variations in different species are due to variations in relative magnitudes and rates of change of these two components (104).

The Ear

Hearing.—Recent references to deafness from injury (105 to 114), particularly blast injury, can be summed up as follows. It is evidently not the increased pressure of the blast *per se*, but the very rapid rate of change of pressure which does the damage

(109). Special emphasis is laid on the suction which follows the pressure component because it lasts three to five times as long as the pressure component (110). Since the tensor tympani reflex has a latent period much longer than the duration of the blast effect it cannot serve to protect the ear from this form of injury (112). The chief effect of blast is rupture of the tympanum (109 to 113, 115), though usually the hair cells of one turn of the spiral organ of Corti (not the whole organ nor the basilar membrane) are destroyed (109), the degree of deafness being greater when the tympanum remains intact than when ruptured (112).

The initial symptom of "sound" injury is depression of sensitivity of the affected ear in one place of the frequence scale, more often about 4096 cps. (113). It is this region which is impaired temporarily in men serving in submarines and at high altitudes, and also in ground forces subjected to explosions. The condition is liable to become permanent and the impairment to spread fanwise to neighboring regions (114). Cats subjected to low barometric pressure show damage to the tympanum and bulla, chiefly vascular changes, viz., congestion with bleeding, edema, and effusion (116).

In guinea pigs, cochlear impairment as a result of intense stimulation at different frequencies is widespread with no specific relation to the exposure frequency. The discrepancy between this and earlier experiments is to be explained in the recent more exact means of producing pure tones at sufficient loudness (117). Malingering can be detected by repeated observations on the subject blindfolded (118).

A good review of methods of examination is given by Levy & Shapiro (119). Bunch's (120) book on *Clinical Audiometry* does not lend itself to a brief review; it is according to Hallowell Davis (121) mostly a personal account of the author's life work. To test the sensitivity of the ear two references are claimed to be necessary, (*a*) the rms (root mean square) pressure of the sound wave at a point in a free sound field where the listener's ear will later be placed; (*b*) pressure at the eardrum. The former is the simpler calculation, the latter presents great technical difficulties. The "phon" as a unit of loudness rather than the decibel is to be preferred (122). Kobrak (123) has been able to make direct observation of movements of the tympanum in living man by means of stroboscopic light reflected to a camera from a mirror on the tympanum. In cadavers acoustic movements of the stapes and basilar membrane can be observed by these means. The point brought out in these exploratory

observations is the importance of the amplitude of over-threshold tones—the author believes that we have too long concentrated on the threshold of hearing.

Accuracy of pitch discrimination is shown to be a function of tonal duration. For 1024 cycles at 60 db. above threshold the effect of duration is slight until the duration is reduced to 0.1 sec.; thereafter discrimination declines rapidly until it reaches 0 around 0.01 sec. For 8192 cycles pitch appreciation is blunted with a duration of less than 0.25 sec., is 0 at 0.02 sec., and for 128 cycles is blunted at 0.5 sec. and is 0 at 0.03 sec. This does not support the theorem that discriminability of pitch varies as the product of intensity in decibels and duration in seconds (124). We are reminded of Galambos' experiments on the supersonic squeaks of bats to avoid obstacles in an article on perception of obstacles by the human blind where aural stimulation is found to be necessary and adequate without the intervention of a supposed pressure sense or stimuli somehow reflected to the skin or face (125). Enthusiastic spouses have welcomed the treatment of snorers whose offending "flutter ratios" have been altered by producing fibrous tissue in the soft palate and surrounding tissues through application of sclerosing substances such as sodium ricinoleate (126).

It seems strange that pitch differences between the two ears (*diplacusis binauralis dysharmonica*) measured at different times should show great enough variations to be of significance, and that diathermy of one ear should produce no consistent shift in pitch difference (127). One individual was found who could voluntarily contract the muscles retracting his tympanum without contracting other muscles in the neighborhood, such as those of the soft palate, etc. The subjective roar corresponded to just above 64 cycles. Loss of hearing gradually decreased at 2048 cycles, with the minimum for the right ear at 7896 and for the left at 4096 cycles (128).

Maps of the acoustic areas of the dog's cortex are similar to those earlier found for the cat, for the details of which the original paper must be consulted (129). In the cat the primary subcortical auditory center lies in the anterior corpora quadrigemina and in the absence of the acoustic cortex approximately normal intensity thresholds are maintained. A rise of 15 db. in threshold was observed after removal of both corpora quadrigemina (130). The guinea pig's cochlea has again been mapped and the spiral of 4½ turns shows straight progress from 60 to 7000 cps in passing from one end to the other (131). The stapes has been fixed in cats' ears

and cochlear responses taken from the round window in this condition. It is found that when the cochlear responses to air conduction are reduced, bone conduction is also reduced; therefore free stapedial motion is important for bone conduction, particularly in the middle range (132). The whole question of the origin of the cochlear response has been gone over by Kellaway (133) who inclines to the view that the phenomenon is a piezoelectric effect, "an epiphenomenon accompanying mechanical distortion of the symmetry of the cells of semisolid nature happening to contain organized oriented molecules." If it has no physiological function can it be used as an index of hearing? The author answers yes, for various reasons, among them the fact that hearing is never demonstrable in the absence of the cochlear response.

The functional anatomy of the auditory tube has been dealt with by Simkins (134) who again describes the flutter valve effect and its passive opening by inequalities of pressure either on the pharyngeal or tympanic side. Mellanby (135) says it is unfortunate that the rôle of vitamin A deficiency in otitis media was first worked out in the rat, since this animal is unique in that A-deficiency causes hyperplasia especially in the auditory tube with resulting infection. This is not the case in children. Deficiency in nicotinic acid, riboflavin, or B are said to affect hearing, though this is unconfirmed. A-deficiency does cause lesions of the acoustic nerve, and overgrowth of the periosteal bone of the labyrinth with degeneration of the spiral organ of Corti.

The labyrinth.—McNally (136) has given us an excellent review of what is known of the functions of the otoliths. Some of the points he brings out are: the saccular otolith is not a part of the equilibrial mechanism; the utricle, on the contrary, is the organ responsible for otolithic reflexes, but it does not respond to rotation about a vertical axis, nor is it proven that it is responsible for nystagmus; the semicircular canals as well as the utricles are concerned with maintenance of postural tone; the utricle is responsible for motion sickness which is the result of linear, not angular, acceleration. McNally calls attention to the lack of really adequate tests. This plaint is reiterated in a Russian article on the effects of anoxemia on the vestibular apparatus (137) in which the authors found that anoxemia produces sharper reflexes, such as pallor, sweating, nausea, in rocking subjects, but were unable to determine specific effects on caloric stimulation of the ear or rotatory stimuli. A re-

view of the best vestibular tests, particularly as used for the armed ferces, is given by Moriconi (138).

The effect of cold on the static receptors of the labyrinth has been studied by Spiegel (139, 140). Cold water in one ear decreases extensor tone on the homolateral side, and affects the position of the head as well as the extremities. This same author (141) finds that puncturing the round window in cats prevents rotation from giving rise to rhythmic ocular movements, but there is still reflex depression of blood pressure to rotation which disappears on application of cocain to the labyrinths. This circulatory reflex must, therefore, originate in the labyrinth. His method of applying cocain and other anaesthetics is most interesting (142). The anaesthetic agent is placed in the external auditory meatus and plugged in by a cotton surrounded electrode (anode); an indifferent electrode is placed on the abdomen; a small current is then applied for five to ten minutes; for the next three to four hours labyrinthine paralysis appears, viz. nystagmus to the opposite side, rotation of the head, pleurothotonus, circus movements, falling to the same side. Investigation (143) has been made of synergistic movements of eyes, face, and ears of rabbits rotated in a horizontal plane. Eyebrows, whiskers, and ears all exhibit movements associated with nystagmus.

Operations on the anterior corpora quadrigemina and occipital lobes in guinea pigs show that whereas the cerebral mechanisms provide the basis for focal pattern vision, the anterior corpora quadrigemina and other primary optic centers provide the basis for pattern vision of moving objects and are, therefore, concerned with nystagmus (144). Menière's disease has recently been reinvestigated and details of the results of the caloric tests of Barany are reported (140). In this disease there are evidently no pathological changes other than in the labyrinth, and whereas formerly surgical treatment consisted in sectioning the VIII nerve, it seems to be better merely to destroy the offending horizontal canal (145, 146).

Zotterman (147) has explored the microphonic effects of the labyrinths of certain fish. The sacculus seems definitely concerned with sound. Rotation gives rise to potentials set off from the ampullae; e.g. the right posterior ampulla gives responses to rotation in an anticlockwise direction; there is no effect on rotation in a clockwise direction until the movement has stopped, when there is afterdischarge.

Taste and Smell

Experimentation on the special senses such as taste in the lower animals demands ingenuity. The "preference" method can be made to yield results so that one can compare such diverse creatures as man, the monkey, and the rat. Using quinine as a test substance, the acceptance threshold of the chimpanzee and monkey is similar to man's at the tip and edge of his tongue, but the rat's acceptance threshold is equal to that at the base of man's tongue, i.e. his most sensitive part (148). This method was used to localize which part of the monkey's thalamus was for taste. The center seems to lie in the arcuate nucleus (149).

A statistical study of olfactory preferences supports the view that as in visual preference judgments there is an "intersensory factor" of "brightness" (150).

Cutaneous Senses

Attention should be called to the papers presented at the symposium on pain (151). This volume forms a valuable addition to the literature on a subject which is paramount to the medical profession.

Bishop has endeavored to solve the eternal problem of the distribution and nature of pain endings in the skin. If a nerve is anaesthetized all except the smallest branch possible, there is found a spot in the skin sensitive to prick surrounded by an area of duller sensitivity. Itch, nonpainful prick, and pain from the same point differ in quality and quantity of sensation (152). If the skin is removed and return of "pain spots" followed, a small area directly above the regenerating nerve twig is found to be more sensitive than the remainder of the area innervated, which may include one to three hair follicles (153). Stimulation by high voltage, low current spark discharges which do not mechanically deform the skin, again show the high spots of extreme sensitivity with surrounding areas of less sensitivity. With this type of stimulus also the same sensory spot can give touch, prick, itch, or sharp pain. The pathway for sensation is evidently multiple from the periphery and the idea that finding a sensory "spot" indicates that this spot is innervated by a single fiber and is connected uniquely to a corresponding spot in the cerebral cortex is characterized as "naive" (154). Exploration of areas of referred pain show that there are "trigger points" in skeletal muscles which cause referred pain and action potentials in the reference zone, e.g., pressure on an irritable spot in the supraspinatus will give rise to action currents in the

deltoid. The responses involve not only skeletal muscle but also arteries in the reference zone (155). A special vibrator, 180 cps, 70 db, has been used to compare the vibration sense under different conditions. This sense belongs to the proprioceptive group and is highest on the finger tips, lowest over the eyelids. In the finger it is found to be diminished when the skin is cold, during general fatigue, and strenuous exercise. It is maximum after refreshing sleep (156).

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METABOLIC FUNCTIONS OF THE ENDOCRINE SYSTEM

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This is a selective critical review of the available articles published between July 1943 and August 1944. Its scope is limited to studies having to do with the biological effects of the hormones. Although an attempt has been made to emphasize those subjects of general interest, the content of this paper has been determined to a significant extent by the interests of the reviewer.

The Anterior Pituitary

The trophic hormones of the anterior pituitary will be considered with the hormones secreted by their "target" organs.

Houssay (1) has reviewed the history of hypophyseal diabetes and Rynearson (2) the clinical use of anterior pituitary hormones.

Li & Evans (3) reported the isolation of a pure form of the pituitary growth hormone. Marx, Simpson & Evans (4) evaluated the specificity of the epiphyseal cartilage test for growth hormone by testing other purified anterior pituitary hormones, and thyroxine. Only purified growth hormone gave a significant response. Marx, Herring & Evans (5) demonstrated that purified growth hormone exerted a hypoglycemic effect in fasting hypophysectomized rats.

Whicher & Watson (6) observed the effects of growth, gonadotrophic and thyrotrophic hormones, and insulin upon the phosphatase content of rat femurs. Both thyrotrophic and gonadotrophic hormones caused an increase in the phosphatase content of the diaphyses and epiphyses. The other hormones failed to produce a consistent effect.

Heinbecker *et al.* (7) found that anterior pituitary extracts increased the diodrast and inulin clearances and the maximum excretion of diodrast at high plasma levels in normal, hypophysectomized, and puncture dogs. Thyroid extract had less effect and adrenal cortical extracts were without a significant effect. Because of the rapid depression of renal function following hypophysectomy it was concluded that anterior pituitary extract has a direct effect upon the kidney.

Elden & Kummer (8) have described a partially hypophysecto-

mized human female having a low metabolic rate, hypotension, hypoglycemia, and atrophy of the thyroid, adrenals, and reproductive organs.

According to Smith & Riddle (9), the hypophysectomized fasting pigeon maintains its stores of tissue glycogen as well as normals and shows a smaller than normal reduction in heat production. Nalbandov & Card (10) noted that young hypophysectomized chicks survived longer than did adults. There was regression of the gonads, thyroids, and adrenal cortices and cessation of skeletal growth.

The hypophysectomized rat shows a voluntary reduction in its intake of food, and this is a factor in causing subsequent metabolic changes. Samuels *et al.* (11) force-fed young hypophysectomized rats an amount of food sufficient to sustain growth in sham-operated controls and observed a very slow increase in skeletal growth, 10 per cent that of the controls, and a very slow increase in nitrogen storage, about 30 per cent that of the controls. The hypophysectomized animals stored more calories due to a greater deposition of fat. However, the liver was higher in protein and lower in fat than the controls. It was concluded that the hypophysectomized rat retains some ability to synthetize structural compounds. Levin (12) found that the weight gains of the force-fed hypophysectomized rat were due to an increased deposition of fat. Skeletal growth was not noted. Contrary to the results of Samuels *et al.* (11) the liver fat was elevated above that of the nonhypophysectomized controls. Hetherington (13) has shown that hypophysectomized rats develop obesity following the production of hypothalamic lesions, thereby adding proof that the hypophysis is not involved in the production of obesity associated with hypothalamic injury.

Moore, Levin & Leathem (14) have confirmed their earlier finding that hypophysectomy results in a fall in serum albumin and a rise in serum globulin.

Shipley (15) demonstrated that anterior pituitary extract stimulated the *in vitro* formation of acetone bodies by rat liver tissue but was without the effect on utilization. It had no effect on the formation or utilization of glucose.

The Adrenocorticotrophic Hormone and the Adrenal Cortex

Several reviews (16 to 20) dealing with the adrenal cortex have

been published during the past year and Goldzieher (21) has published a book on the adrenal glands.

Li, Evans & Simpson (22) and Sayers, White & Long (23) have each given a full description of their isolation of pure adrenocorticotrophic hormone. Tyslowitz (24) prepared an extract of hog pituitary glands which passed through a cellophane membrane and retained adrenocorticotrophic activity. Simpson, Evans & Li (25) have developed two methods for the assay of adrenocorticotrophic hormone. One method ascertains the total dose required to cause beginning redistribution of cortical lipid in female rats (twenty-six to twenty-eight days old at hypophysectomy) in which the four-day injection period is begun fourteen days following hypophysectomy. The second method determines the daily dose of hormone necessary to maintain the preoperative adrenal weight for fifteen days, in male rats hypophysectomized at forty days of age. A statistical evaluation of the sensitivity and reliability of the methods has not yet been presented. Koneff (26, 27) found that the administration of adrenocorticotrophic hormone to either normal or adrenalectomized rats caused a decrease in the weight of the hypophysis with accompanying cytological changes in the cells. Fraenkel-Conrat *et al.* (28) found that treatment of hypophysectomized rats with pure adrenocorticotrophic hormone for fourteen days increased the insulin content of the pancreas. Haist & Bell (29) concluded that the production and liberation of insulin can be regulated in response to diet changes in the absence of the adrenals or the gonads.

Secretory activity of the adrenal cortex.—Up to the present there has been no direct method of estimating the amounts of hormones secreted by the adrenal cortices. A study by Vogt (30) may have opened the way for an investigation of this problem. Blood was collected from the adrenal vein in dogs, cats, goats, rabbits, and pigs and the serum was assayed for cortical hormone activity by the Selye-Schenker cold test. As judged by this criterion the hormone content of the adrenal venous blood was invariably high but it could not be detected in arterial blood or in blood from the right side of the heart. It was estimated that the daily output of both adrenal glands of a 10 kilogram dog was the equivalent of 230 cc. of a commercial adrenal extract or of 17,300 gm. of beef adrenal glands. It was concluded that the cortical hormone is rapidly inactivated by the tissues. This interesting study will require confir-

mation based upon purification of the hormone and testing by other methods of assay before the results are likely to be generally accepted.

Sayers *et al.* (31, 32) observed that a single dose of pure adrenocorticotrophic hormone in the rat diminished adrenal cholesterol from one-half to two-thirds of its normal value within three hours, after which recovery occurred. The prolonged administration of adrenocorticotrophic hormone raised the total cholesterol content of the cortex, due in part to hypertrophy. Because of the close chemical relationship between cholesterol and the cortical steroids it is possible that the changes in adrenal cholesterol may reflect changes in the biosynthesis or secretion of the cortical hormones as induced by the adrenocorticotrophic principle.

It is not within the scope of this review to give a full consideration to the excretion products of the hormones. However, the excretion of neutral 17-ketosteroids and cortin-like substances in urine has become of interest to both the physiologist and the clinician as indices of the secretory activity of the adrenal cortices. Venning, Hoffman & Browne (33) have reviewed the evidence that the neutral 17-ketosteroids are derived from the adrenal cortex as follows: (*a*) certain 17-ketosteroids have been isolated from the adrenal cortex; (*b*) male and female castrates excrete significant amounts of 17-ketosteroids; (*c*) patients having tumors of the adrenal cortex with symptoms of hypercorticosuprarenalism usually excrete larger then normal amounts of 17-ketosteroids; and (*d*) patients with Addison's disease excrete very small amounts of 17-ketosteroids. This indirect evidence provides support for the view that the neutral 17-ketosteroids are metabolites of some of the cortical steroids and that the amounts excreted provide a criterion of the secretory activity of the gland. Direct evidence of the kind which would be required for proof of the theory is lacking. The metabolism of the cortical steroids is inadequately understood.

Three principal lines of evidence support the view that the amount of cortin-like material excreted in urine provides an index of the secretory activity of the adrenal cortices: (*a*) following a stress there is a significant increase in the excretion of cortin-like material in human urine (33); (*b*) the administration of adrenal cortical extracts and steroids is followed by an increased excretion of biologically active material in urine; and (*c*) cortin-like material cannot be recovered from the urine of animals or patients having

adrenal cortical insufficiency. Shipley, Dorfman & Horwitt (34) demonstrated that the cortin-like material of normal male urine was active in a muscle work test and Schiller & Dorfman (35) found that it raised the resistance of adrenalectomized rats to water intoxication. Dorfman *et al.* (36) demonstrated urinary cortin-like material in normal and gonadectomized but not in adrenalectomized monkeys. Injection of cortical extracts to adrenalectomized monkeys was followed by the excretion of active material but in only one instance was it demonstrable after the administration of 11-desoxycorticosterone acetate.

The hypothesis that the amount of cortin-like material in urine can serve as an index of the secretory activity of the adrenal cortex is based in part on the unproven assumption that a constant proportion of the hormones secreted by the glands is excreted in active form in urine. Caution is indicated since only a small proportion of the biological activity of cortical extracts given to humans (33) or monkeys (36) was recovered in the urine.

Effects of adrenocorticotrophic and adrenal hormones on the lymphatic system.—Many investigators have reported on the enlargement of the thymus following adrenalectomy in the rat. Stoerk (37) observed that the thymus glands of adrenalectomized rats were larger than normal when the animals were fed the Rockland diet but were not larger than those of normal rats fed diets optimal for growth. It was concluded that the thymus glands of the adrenalectomized rats were not hyperplastic but that those of the normals manifested partial atrophy due to the stress of the suboptimal diet and that this partial atrophy was dependent upon an increased secretion of cortical hormones. The experimenter did not report data on the effect of adrenalectomy on thymus size in rats on the so-called optimal diet and did not consider the data and diets of other investigators to determine whether their results might fit his hypothesis.

Dougherty & White (38) found that pure adrenocorticotrophic hormone produced a decrease in the weight of the various lymph nodes as well as the thymus in normal mice. Similar observations were made by Simpson *et al.* (39) in rats. White & Dougherty (40) observed that single injections of either adrenocorticotrophic or cortical extracts into mice or rabbits caused within one to three hours degenerative changes in the lymphoid tissue of thymus and lymph nodes. Elevations in serum protein accompanied the involu-

tion of lymphoid tissue. It was suggested that lymphoid tissue may serve as an important source of protein for gluconeogenesis during the action of increased amounts of cortical hormones.

Dougherty & White (41, 42) have shown that the administration of pure adrenocorticotrophic hormone, cortical extracts, and C-11 oxygenated steroids to mice, rats, and rabbits caused an absolute lymphopenia within a few hours but that 11-desoxycorticosterone acetate was ineffective. Dougherty, White & Chase (43) observed that agglutinin titers to sheep erythrocytes in the rabbit were enhanced as a result of cortical extract injection. The titers were increased within six hours after the injection of adrenal cortical extract into hyperimmunized rabbits.

Murphy & Sturm (44) noted that adrenalectomized rats had an increased susceptibility to inoculated leukemia and that when intact rats were inoculated with leukemic cells (45) the administration of cortical extracts, 11-desoxycorticosterone acetate, or adrenocorticotrophic hormone caused a significant increase in the incidence of survival among treated animals.

Heilman & Kendall (46) administered 17-hydroxy-11-dehydrocorticosterone to young mice which were hosts to implanted highly malignant tumor cells, probably lymphosarcoma, and found that the tumors failed to develop or that regression occurred in previously established tumors. The effect was temporary and all of the animals eventually died from the effect of the tumors.

The adrenal cortex in relation to conditions of stress.—No convincing evidence has been forthcoming to show that any of the cortical hormones will protect animals or patients having undamaged adrenal glands against naturally occurring forms of shock. Swingle *et al.* (47) investigated the value of cortical extracts and of 11-desoxycorticosterone acetate in the treatment of shock in nonadrenalectomized dogs. Shock was induced by limb ligation, trauma to the hind legs, and venous occlusion of one hind leg. The results were negative. Prinzmetal *et al.* (48) concluded that neither 11-desoxycorticosterone nor cortical extracts were effective in protecting intact rats and mice against burn shock. Rhoads *et al.* (49) administered cortical extracts to twelve patients with extensive superficial burns and found that they did not retain plasma given by transfusion any better than did thirteen control patients. These results are in contradiction to the frequently quoted favorable results reported earlier by Rhoads *et al.* (50). Fowler (51)

produced shock in intact dogs by the intraperitoneal implantation of muscle. No protection was afforded by either 11-desoxycorticosterone acetate or cortical extracts. Huizenga, Brofman & Wiggers (52) reported on the ineffectiveness of adrenal cortex extracts in standardized hemorrhagic shock in dogs. Cope & Moore (53) studied capillary permeability in experimental burn shock in nonadrenalectomized dogs by injecting radioactive colloids and measuring their appearance in the lymph. Adrenal cortical extract exerted no detectable effect on capillary permeability.

Certain unnatural conditions of stress can be set up in the laboratory in which the resistance of nonadrenalectomized animals can be increased by the administration of cortical hormones. Lowenstein & Zwemer (54) found that 11-desoxycorticosterone acetate raised the resistance of normal rats to potassium poisoning. Reiss, Macleod & Golla (55) reported that the resistance of normal rats to shock induced by the intraperitoneal injection of hypertonic glucose solutions was increased by the administration of either 11-desoxycorticosterone acetate or of adrenocorticotrophic hormone. The reviewer does not regard the data given in support of this conclusion as convincing. Gaunt (56, 57) has demonstrated that normal rats can be protected against water intoxication with either 11-desoxycorticosterone acetate or cortical extracts. All of the treated animals survived the largest dose of water given to any of the controls, all of which died. The treated animals showed a better maintenance of body temperature, rate of diuresis, and freedom from the typical convulsions of water intoxication.

Darrow & Sarason (58) subjected rats to prolonged exposure at low atmospheric pressures. No adrenal cortical hypertrophy was observed. These authors questioned the validity of the results of earlier studies showing cortical hypertrophy due to anoxia. In the opinion of the reviewer, it has been well proven that anoxia can cause adrenal cortical hypertrophy. In studies by Hailman (59) on the factors involved in adrenal cortical hypertrophy due to anoxia it was shown that when acapnia was prevented hypertrophy did not occur; subdiaphragmatic vagotomy (60), believed to abolish the vagoinsulin response to low pressures, did not prevent hypertrophy; and that the administration of large amounts of riboflavin or vitamins of the B-complex (61) failed to prevent hypertrophy.

Some investigators have reported that anoxia causes hyperglycemia and others have stated that hypoglycemia results. Van

Middlesworth, Kline & Britton (62) studied carbohydrate regulation during severe anoxia in rats. Rapidly induced anoxia caused hyperglycemia for periods up to one hour, due apparently to stimulation of the adrenal medulla as it did not occur in adrenalectomized animals. In normal rats fasted for twelve hours the initial hyperglycemia was followed by hypoglycemia, but in fed animals, animals fasted for long periods, and in acclimatized animals hypoglycemia did not occur.

Hartman & Brownell (63) investigated the response of adrenalectomized cats to chilling. The rectal temperature fell more rapidly in adrenalectomized animals than in normals, the increases in blood glucose due to chilling were usually less than normal, and the arterial pressures fell to subnormal levels. There were no significant changes in the plasma sodium or chloride.

Roos (64) described a method for assay of cortical extracts based upon the maintenance of body temperature of young adrenalectomized rats exposed to cold. Large numbers of animals were required, it was necessary to record body temperatures frequently, and it was not possible to construct a dose-response curve. Ingle (65) has given a detailed description of his work test for the assay of the "carbohydrate" type of activity possessed by the C-11 oxygenated steroids. The test is too complex for general use.

Vögtli (66, 67) has published two papers dealing with Ingle's work test in which the conclusion was reached that the test is invalid as a measure of cortical hormone activity. Although the methods and apparatus used by Vögtli were alleged to be identical with those of Ingle there was only a superficial similarity between them. Stimulation by an inadequate method was continued for only eight hours whereas Ingle has repeatedly emphasized that prolonged stimulation by a severe shock is required to test the endurance of the animal. Vögtli stated that sham-operated as well as adrenalectomized rats develop operative shock independently of adrenal cortical insufficiency, but he ignored all of the control data on sham-operated animals published by Ingle. Vögtli concluded that 11-desoxycorticosterone was able to sustain the ability to work in adrenalectomized rats treated for several days prior to the beginning of the work test just as effectively as adrenal cortical extracts and that the only difference between the action of this steroid and that of the C-11 oxygenated compounds is due to differences in the rate of absorption. Vögtli ignored the studies by

Ingle (68) on rats pretreated for seven days with 11-desoxycorticosterone and 17-hydroxy-11-dehydrocorticosterone and a study (69) on the ineffectiveness of a water soluble form of 11-desoxycorticosterone and reached conclusions regarding the comparative efficacy of 11-desoxycorticosterone and the C-11 oxygenated steroids without experience with the latter compounds. It is the opinion of the reviewer that the data of these papers do not seriously challenge the generally accepted conclusion that 11-desoxycorticosterone differs qualitatively in its biological properties from the C-11 oxygenated compounds.

The effect of adrenocorticotrophic and cortical hormones on the metabolism of carbohydrate, protein, and fat.—Evans, Simpson & Li (70) administered pure adrenocorticotrophic hormone to normal and castrated male rats and observed inhibition of growth. In adult rats a loss of weight occurred. Marx *et al.* (71) demonstrated an antagonistic effect of adrenocorticotrophic hormone to pituitary growth hormone in hypophysectomized rats, and Becks *et al.* (72) observed that the antagonism involved the osseous system. Adrenocorticotrophic hormone alone had little effect upon the proximal epiphyseal regions of the tibia. Growth hormone activated the cartilage and caused formation of trabeculae. When the hormones were given in combination there was retardation of bone formation. The administration of adrenocorticotrophic hormone to normal rats also inhibited bone growth (73). It is probable that these effects of the adrenocorticotrophic hormone are mediated by an increased secretion of certain adrenal cortical steroids. It is known that the C-11 oxygenated compounds inhibit growth in rats but only in large doses. Kuizenga, Nelson & Ingle (74) have shown that the treatment of young adrenalectomized rats with 17-hydroxy-11-dehydrocorticosterone at levels of 0.05 to 1.0 mg. daily permitted growth at a subnormal rate.

What is the mechanism by which the cortical steroids affect growth? Heretofore the emphasis has been upon the hypothesis that the C-11 oxygenated adrenal steroids affect growth processes indirectly by increasing the catabolism of proteins and thereby making less protein available for tissue synthesis. Some stimulating new concepts were introduced by Albright (75) in his Harvey Lecture for 1943. His paper includes a comprehensive discussion of the possible role of the adrenal cortical hormones in the etiology of Cushing's syndrome. This disease is characterized by a depletion

of the tissues of bone, skin, and muscle which Albright attributes to an excess of the C-11 oxygenated cortical steroids. The primary action of these hormones upon protein metabolism is regarded as "anti-anabolic" or growth-inhibiting rather than "catabolic." As evidence against the "catabolic" theory it was pointed out that patients with Cushing's syndrome are usually in a slightly positive nitrogen balance although there is evidence that early in the disease there is a temporary period of a strongly negative nitrogen balance. Also, if the fundamental disturbance were an increased conversion of proteins into sugar the minimum nitrogen excretion during a high caloric intake of carbohydrate and fat should be greater than normal, whereas they were found to be normal or less than normal. These facts can be explained by the "anti-anabolic" theory which would also account for the growth-inhibiting effect of the C-11 oxygenated compounds and adrenocorticotrophic hormone. In unpublished studies, the reviewer has shown that during the prolonged administration of 17-hydroxycorticosterone or of 17-hydroxy-11-dehydrocorticosterone to rats there was first a sharp increase in nitrogen excretion correlated with cessation of growth and loss of weight, but that later a positive nitrogen balance was regained although growth, when it occurred at all, was subnormal. How can the initial negative nitrogen balance and increased formation of carbohydrate be due to an "anti-anabolic" effect? Since the proteins of the tissues are in a dynamic state of continuous breakdown and resynthesis, Albright assumes that the blocking of resynthesis by the action of the cortical hormones would tend to deplete the tissue proteins and make greater amounts available for gluconeogenesis. Why would not this initial negative nitrogen balance continue indefinitely? Albright assumes that after a marked depletion of the tissues has occurred a certain amount of adaptation takes place so that a slightly positive balance between catabolic and anabolic processes can be reestablished.

The reviewer is not convinced that the known effects of the C-11 oxygenated compounds are inexplicable by the "catabolic" hypothesis. Any hypothesis must account for the apparent fact that during the course of hyperadrenocortinism there is a shift from a strongly negative nitrogen balance to a slightly positive nitrogen balance. It must be assumed that some adaptation has occurred. This assumption can be embodied in one hypothesis as well as in the other. The "catabolic" hypothesis derives some sup-

port from those studies, recently reviewed by Long (76), which have indicated that the C-11 oxygenated steroids increase the rate of conversion of compounds derived from protein into carbohydrate.

Herring & Evans (77) have shown that the property of maintaining the muscle glycogen of hypophysectomized rats was greatest in crude anterior pituitary extracts and in the purified growth fraction. The adrenocorticotrophic hormone, cortical extracts, and 17-hydroxy-11-dehydrocorticosterone caused appreciable increases in muscle but not in liver glycogen. The extent of response to these hormones was dependent upon the duration of treatment.

Russell (78) studied the effect of the presence or absence of anterior pituitary and cortical hormones in the eviscerated rat. The glucose utilization of either hypophysectomized or nonhypophysectomized eviscerated rats was depressed by crude anterior pituitary extract. Both hypophysectomized-eviscerated and adrenalectomized-eviscerated rats utilized more glucose than did eviscerated rats but utilization could be inhibited to some extent by cortical extracts.

Thorn & Clinton (79) administered 33 mg. of 17-hydroxy-11-dehydrocorticosterone in a single dose to a young male patient having coexisting diabetes mellitus and Addison's disease. There was an elevation of blood glucose, lowering of the respiratory quotient, and increased excretion of glucose, nitrogen, phosphorus, sodium, chloride, and ketone bodies.

In a series of studies on carbohydrate metabolism in adrenalectomized cats and dogs, Montigel & Verzar (80, 81, 82) and Montigel (83) have drawn support for their conclusion that 11- desoxycorticosterone will fully replace the functional activity of the adrenal cortices and that it is concerned with phosphorylation processes. These conclusions are opposed by the results of many careful investigations from other laboratories and clinics. As reviewed by Anderson (17), the absorption, transport, and deposition of carbohydrate in tissues may be normal in adrenalectomized animals which are maintained in good condition by a favorable intake of electrolytes. These phases of metabolism are also essentially normal in animals treated with 11-desoxycorticosterone. But it has been established beyond reasonable doubt that the compound 11-desoxycorticosterone is deficient in its ability to stimulate the formation of new carbohydrate from noncarbohydrate sources.

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Vogt (84) studied the carbohydrate metabolism of the isolated intestine of the rabbit and found no change from normal during adrenal insufficiency.

Samuels & Conant (85) fed high fat diets to normal and adrenalectomized rats. In the adrenalectomized animals fed butter-fat the acetonuria was less than normal and the liver fats fell more rapidly during fasting, but the depot fats were used at a slower than normal rate. When tung oil was used in the diet the ketonuria was increased in all animals and the liver fats of both normal and adrenalectomized animals fell at an equally rapid rate. These authors suggested that in adrenalectomized rats the deficiency is in the transport of fat from the depots to the liver. Bavetta (86) found that caprylic and capric acids were absorbed more slowly by adrenalectomized than by normal rats and has reaffirmed his belief that there is a defect in fat absorption during adrenal cortical insufficiency in the rat. The reviewer (18) is not convinced that it has been possible to discriminate between "primary" and "secondary" causes of altered fat metabolism in adrenal cortical insufficiency.

Broda (87) estimated that approximately 30 per cent of the ketone content of the blood was removed by the passage of the blood through the adrenal glands of the dog as was evidenced by the lower values for ketones in the blood of the adrenal vein as compared to that of the adrenal artery.

The adrenal cortical hormones and electrolyte and water balance.— Rice & Richter (88) found that normal male rats showed a seven fold increase in voluntary consumption of a sodium chloride solution when injected with 2 to 4 mg. of 11-desoxycorticosterone acetate daily. In confirmation of Richter & Eckert (89) it was shown by Mark (90) that the high intake of sodium chloride by adrenalectomized rats was reduced to normal during treatment with pellets of 11-desoxycorticosterone acetate. This apparent reversal of the effect of 11-desoxycorticosterone upon appetite for sodium chloride is probably conditioned by the size of dose. Winter & Ingram (91) studied the polyuria produced by the administration of 11-desoxycorticosterone acetate in relation to the diabetes insipidus resulting from posterior pituitary deficiency and concluded that the cortical hormones do not participate in the establishment of diabetes insipidus of posterior pituitary origin.

Gaunt (57) demonstrated that following adrenalectomy in the rat there was a prompt diminution in the diuretic response to

water intoxication. The lack of water diuresis appeared to have been due to a delayed absorption of water from the gastrointestinal tract and an inability to excrete the water that was absorbed. Whereas normal rats lost chloride by excretion, the adrenalectomized rats lost large amounts into the unabsorbed fluid of the gut. Stein & Werthheimer (92) observed that the urine excretion of adrenal demedullated rats was abnorally low following the oral administration of water but was restored by either epinephrine or massive doses of 11-desoxycorticosterone acetate. It was concluded that the changes were due to the absence of the adrenal medulla. No reference was given to the earlier study by Eversole, Edelmann & Gaunt (93) who reported that the decreased resistance of adrenal-demedullated rats to water intoxication and the decrease in diuresis could be restored to normal by treatment with cortical extract. The reviewer now believes, contrary to his earlier opinion, that the procedure of adrenal demedullation may possibly cause a prolonged decrease in the functional capacity of the adrenal cortices. Further studies of this problem are indicated. Samuel, Schweizer & Gaunt (94) found that hypophysectomized rats developed hemoconcentration and shock which was prevented by cortical extracts and 11-desoxycorticosterone acetate. Both hypophysectomized and normal rats differed from adrenalectomized rats in that the latter failed to show an initial transfer of fluid, electrolytes, and protein to the peritoneal cavity.

Graham (95) noted that irradiation of either normal or adrenalectomized dogs with a carbon arc lamp produced a fall in blood pressure which was diminished or prevented by the administration of either 11-desoxycorticosterone acetate or cortical extracts. The dosages were not given. Graham (96) also observed that irradiation of the rabbit with a carbon arc lamp caused changes which allowed an increased amount of trypan blue to leave the blood and infiltrate the tissues. The administration of large doses of either 11-desoxycorticosterone acetate or cortical extract inhibited or prevented the effects of irradiation on capillary permeability.

Chambers & Cameron (97) noted that the secretory activity of the renal proximal tubules of the chick embryo in tissue culture was stimulated by cortical extracts and by 17-hydroxy-11-dehydrocorticosterone but not by 11-dehydrocorticosterone or by Kendall's amorphous fraction. An attempt was made to link these observations to the different types of action of these hormones on

metabolic processes by stating that 11-dehydrocorticosterone has the greater effect upon the metabolism of inorganic salts whereas 17-hydroxy-11-dehydrocorticosterone, the efficient agent in the renal secretory mechanism which is intracellular, is known to enhance carbohydrate metabolism. This explanation is not fully convincing since 11-dehydrocorticosterone also affects carbohydrate metabolism and the amorphous fraction has been described by Kendall (98) as the most effective in influencing renal function.

Cicardo (99) found that adrenalectomy in the toad caused a marked decrease in the sodium of skeletal muscle but that liver sodium remained normal. Ziegler, Anderson & McQuarrie (100) treated normal rats with 11-desoxycorticosterone and found a significant reduction in the potassium content of brain and liver tissue without change in sodium and water.

Selye and co-workers (101 to 105) have demonstrated that over-dosage with 11-desoxycorticosterone acetate in various species combined with a high intake of sodium chloride caused pathological changes simulating periarteritis nodosa, renal hypertension, and rheumatic lesions in human patients. These effects could be duplicated (106) by anterior pituitary extracts. It was emphasized that the development of these diseases in humans is usually preceded by infections, exposure to cold, or other damaging agents which may activate the adrenal cortices to secrete damaging amounts of their hormones. This hypothesis should be considered cautiously. The importance of 11-desoxycorticosterone as a naturally occurring hormone of the adrenal cortex is uncertain. Massive doses of the steroid were administered in these experiments and damaging effects were evident only when the intake of sodium chloride was high. Moreover, Selye's own classical studies (107) which demonstrated the nonspecificity of damaging agents may be relative to the present problem.

Several investigators have previously demonstrated the damaging effects of 11-desoxycorticosterone in animals on a low potassium diet. Darrow (108) has shown that a combination of a low potassium diet and injections of 11-desoxycorticosterone acetate produced in four days a loss of potassium and gain of sodium by the rat heart. Heart lesions were produced within one week by this treatment. Goodof & MacBryde (109) treated a young female patient having Addison's disease with cortical extracts and 11-desoxycorticosterone acetate. The patient died in cardiac failure and

at autopsy the heart showed foci of necrosis of cardiac muscle similar to those described in animals on a low potassium intake or given 11-desoxycorticosterone acetate. It is evident that the dietary intake of both sodium and potassium is important in determining the damaging effects of 11-desoxycorticosterone.

Miscellaneous observations on the adrenal cortical hormones.—Tipton (110) found a decrease of cytochrome oxidase and cytochrome-*c* in the liver, kidney, and heart of adrenalectomized rats. Treatment with sodium chloride prevented some and treatment with cortical extract prevented all of the decrease. Riddle *et al.* (111) demonstrated that young adrenalectomized pigeons showed little or no change from normal in heat production.

Chauchard *et al.* (112) found that in young rats adrenalectomy was followed by increases in central and peripherial nerve chronaxia. Muscle chronaxia was not increased. The administration of 11-desoxycorticosterone acetate restored the chronaxia of nerve to normal and in some cases decreased it below normal. Chauchard (113) observed that small doses of 11-desoxycorticosterone acetate in normal rats and guinea pigs caused a slight decrease in peripheral and central nerve chronaxia, while large doses caused general depression with a large increase in nerve chronaxia. All doses caused a decrease in muscle chronaxia.

Anderson *et al.* (114) reported that rats having renal hypertension showed a fall in blood pressure following total hypophysectomy, which was restored by treatment with pure adrenocorticotrophic hormone.

In confirmatory studies, Marshall (115) observed that all the tissues of the rat with the exception of the whole gut and stomach showed a significant increase in histamine content following adrenalectomy.

Gitman *et al.* (116) and Perera & Parker (117) have reported cases of coexisting Addison's disease and hyperthyroidism. Darrow (118) described a male infant having coexisting adrenal cortical insufficiency and virilism.

The Adrenal Medulla

Ranges & Bradley (119) studied the circulatory changes induced by epinephrine in male convalescent patients. Epinephrine caused vasodilatation with an increase in cardiac output associated with increased intra-atrial pressure thereby producing pressor ef-

fects. The renal plasma flow was decreased without a change in the glomerular filtration rate and the filtration fraction increased indicating efferent arteriolar vasoconstriction. Froster (120) tested the effects of epinephrine upon renal hemodynamics in the intact frog. Small amounts caused a decrease in blood flow and an increase in the filtration fraction but the rate of glomerular filtration remained constant. These effects resulted from constriction of the efferent glomerular tubule. Massive doses caused a decrease in blood flow, filtration fraction, filtration rate, and in the number of functioning glomeruli.

Deichmann (121) confirmed Richter (122) in showing that epinephrine is inactivated *in vivo* by conjugation as was evidenced by a markedly augmented excretion of organic sulfates following the administration of epinephrine to the rabbit.

Perry (123) administered epinephrine to female rats and observed regression in the reproductive system. The results were interpreted as indicating a specific relationship between epinephrine and the reproductive system of the rat. No consideration was given to the possible explanation that the response was that of a mild nonspecific damaging agent (107).

Sayers *et al.* (124) found that adrenal demedullation resulted in a normal glucose tolerance in rats showing a hereditary "diabetes." The administration of epinephrine with glucose produced a diabetic type of glucose tolerance curve in the adrenal demedullated rats. These results indicate a relationship between the adrenal medulla and the "diabetic tendency" observed in this (Yale) strain of rats. The authors acknowledged the possibility that adrenal demedullation may have resulted in a decreased function of the cortices.

Fuhrman *et al.* (125) noted that the response of the nictitating membrane of the cat to epinephrine became progressively greater as the body temperature was reduced. Friedenwald & Buschke (126) showed that excitation of rats diminished the mitotic rate in the corneal epithelium. The change in mitotic rate was found to be an adrenergic response which could be simulated by either the local or the systemic application of epinephrine.

Posterior Pituitary

Chen & Geiling (127) have reported on the chemistry and pharmacology of the melanophore hormone. A method of assay was

described which is based upon the melanophore response in the hypophysectomized frog. Ham (128) found that, in agreement with Silvette (129), extracts of the posterior pituitary could be assayed more accurately by measuring urinary chloride excretion than by measuring inhibition of water excretion. Thompson (130) used the blood pressure of the chick for testing the oxytocic activity of posterior pituitary extracts.

According to Sawyer & Ettinger (131, 132), the continuous infusion of dilute posterior lobe extract in the normal dog slowed the heart beat to about half of the normal resting rate. The inhibitory effect was shown to be produced entirely through the inhibitory fibers of the vagus and sympathetic nerves. In confirmatory studies, Ogden, Page & Anderson (133) demonstrated that renal hypertension could be induced in rats following removal of the posterior pituitary.

Wislicki (134) investigated the antagonism between the posterior pituitary hormones and insulin in the rabbit. Both pituitrin and pitressin in large doses caused a transitory hyperglycemia but pitocin was without effect. Very large doses of pituitrin inhibited the hypoglycemic effect of small doses of insulin. The action of pitressin was less marked and pitocin was ineffective. It was concluded that pituitrin contains a principle which is concerned with anti-insulin action other than pitressin or pitocin.

Silvette (135) demonstrated that the polyuria induced by low atmospheric pressure in the rat could be inhibited by the injection of posterior pituitary extracts. Fugo (136) found evidence that the antidiuretic action of yohimbine in dogs was mediated by the antidiuretic hormone of the posterior lobe. Heller (137) tested the hypothesis that the high dilution of the urine of newborn infants results from some inadequacy of the posterior pituitary renal mechanism. It was shown that intramuscular injections of posterior pituitary extract in doses which inhibited water diuresis in the adult had only a slight effect upon the hypotonic urine of infants. It was suggested that there is a low sensitivity of the renal tubules of newborn children to the posterior pituitary antidiuretic hormone.

The Pancreatic Islets

Lukens (138) has reviewed the clinical and experimental data relating to the etiology of diabetes mellitus and Joslin (139) has

summarized recent developments in the field. Houssay (140) has reviewed the known effects of hyperthyroidism and hypothyroidism on carbohydrate metabolism, diabetes mellitus, and the action of insulin. The relation of insulin to phosphate metabolism has been considered by Stadie (141). It was concluded that there is substantial evidence that insulin affects the metabolism of phosphate but that the precise chemical mechanisms are unknown.

Alloxan diabetes.—During the past year a number of papers have been published confirming the production of alloxan diabetes in dogs (142, 143, 144), rabbits (142, 145 to 150), and rats (142, 143, 146, 147, 151, 152). Brunschwig *et al.* (153) administered alloxan to a patient with hyperinsulinism resulting from islet cell carcinoma. Temporary relief from hypoglycemia was obtained after each series of injections. Necrosis of the malignant islet cells was found at autopsy.

There is good agreement among investigators that alloxan diabetes is due to a direct damaging effect upon the beta cells of the islets resulting in a decreased ability to secrete insulin. Hughes, Ware & Young (146) have given the most complete analysis of the changes occurring following the administration of alloxan in rats and rabbits. Changes in the islet tissue were observed within five minutes following the intravenous administration of 300 mg. of alloxan per kg. in the rat. Small fragments of cytoplasm were cast from the surface of the cells and found to lie in the pericapillary tissue. The damage was limited principally to the beta cells. The largest islets showed the greatest damage. These authors postulated that following the administration of alloxan the initial hyperglycemia is due to the release of epinephrine, the temporary hypoglycemia which follows is due to the release of insulin from the dead or dying islet cells, and the later development of diabetes mellitus to insulin lack. It was found possible to duplicate the blood sugar response of the rabbit to alloxan by injections of epinephrine and protamine zinc insulin. Earlier studies were quoted in which alloxan had been found in the urine of humans, thereby giving some basis for the hypothesis that this substance might play a role in the etiology of human diabetes.

Ridout *et al.* (143) found that alloxan did not exert a hypoglycemic effect in either depancreatized dogs or dogs previously made diabetic by alloxan. It was concluded that the hypoglycemia following the administration of alloxan was caused by the release of

insulin by the dead islet cells. Goldner & Gomori (149) studied the mechanism of alloxan diabetes in rabbits. The initial hyperglycemia was prevented by giving insulin and the hypoglycemic phase was prevented by injections of glucose, but the damage to the beta cells still occurred. It was further shown that alloxan did not inhibit the action of insulin. Hard & Carr (150) have stated that the values for liver glycogen and fat remained normal within the period of three hours to twenty-five days following the administration of alloxan in rabbits. No data were given. Bailey, Bailey & Leech (147) described the development of bilateral diabetic cataracts in rabbits within four to six weeks following the onset of alloxan diabetes and the occurrence of cataracts and of diabetic acidosis and coma in the rat.

Diabetes mellitus.—Dosne (154) used a new technique for partial pancreatectomy in the toad which does not damage the circulation and permits prolonged survival. In such animals, a diabetic state developed and persisted during the winter months but in summer the remaining islets showed hyperplasia and the diabetes disappeared. Hypophysectomy prevented the development of diabetes but it could be reinduced by the injection of anterior lobe tissue. Adrenalectomy also provented the development of diabetes and the injection of pituitary anterior lobe tissue reinduced the diabetes in the absence of the adrenals. Pancreatic diabetes in the toad was not modified by thyroidectomy. De Finis & Houssay (155) found that thyroidectomy did not effect the development of diabetes in the depancreatized dog but that the administration of thyroid substance aggravated pancreatic diabetes. Foglia & Cramer (156) reported that the incidence of cataracts in the partially depancreatized rat was related to the severity of the diabetes.

Houssay, Dosne & Foglia (157) found that eviscerated dogs required 100 to 200 mg. of glucose per kg. per hour for the maintenance of blood sugar level. Utilization values for eviscerated dogs having an additional pancreatectomy or having been made previously diabetic by anterior pituitary extracts were within the normal range but tended to be higher than normal. The same was true of dogs treated with the thyroid hormone. Thyroidectomy did not modify glucose utilization. These investigators have questioned whether the eviscerated dog can be regarded as normal except for deprivation of the liver and viscera.

Root (158) studied the effect of glucose administration during

diabetic acidosis in patients. There was no increase in the respiratory quotient following the administration of glucose but it did rise following treatment with insulin. Mirsky & Nelson (159) investigated the basis for the greater tendency of children to develop acidosis than do adults. Normal and diabetic children were studied by means of a phlorhizin test which these authors believe to be effective in draining out the liver glycogen. Phlorhizin glycosuria in either normal or diabetic children was followed by hypoglycemia and a compensatory ketonemia. The younger the child the smaller the relative amount of hepatic glycogen which accounted for the inverse relationship between the age of children and the incidence of ketonemia.

Effects of insulin.—Reiner *et al.* (160) studied in rabbits the absorption rates of different forms of insulin which were labeled with radioactive iodine. The decrease in radioactivity at the site of injection was the index of the rate of absorption. The order of rapidity of absorption was regular insulin, globin insulin, and protamine zinc insulin. Root *et al.* (161) used the same procedure to study the rate of absorption of insulin in human patients. In uncomplicated diabetes the absorption rate of insulin was normal but patients with idiopathic insulin resistance showed a significant delay in absorption.

Sacks (162) observed that the injection of insulin into cats caused a marked increase in the turnover rates of phosphocreatine and adenosinetriphosphate in resting muscle during glucose absorption, as determined by radioactive phosphorus, but there was no increase in the turnover of glucose-6-phosphate beyond that produced by glucose alone. It was postulated that the increased turnover was associated with the increased oxidation of glucose which insulin produced in resting muscle. Rice & Evans (163) studied the respiration of minced pigeon breast during the period when the insulin effect was present. Insulin caused an increased oxygen uptake by the muscle mince and an increased utilization of pyruvic acid. The utilization of pyruvate was inhibited by malonate and restored by the addition of fumarate and pyruvate and of pyruvate plus oxaloacetate. Both of these reactions were accelerated by insulin but the hormone was without effect upon the oxidation of citrate and α-ketoglutarate acids. It was suggested that, in addition to its *in vitro* effect upon the oxidation of pyruvic acid, insulin is concerned with the maintenance of the functional integrity of either

one or both of the enzyme systems involved in the reactions of fumaric and pyruvic acid or of oxaloacetic and pyruvic acid.

In a study on fasted rats given radioactive phosphate, Kaplan & Greenberg (164) found that insulin caused a shift of phosphate from the serum to the liver. Both insulin and glucose caused an increase in the radioactive adenosinetriphosphate and a decrease in the residual and alcohol-soluble radioactive phosphorus of the liver. Insulin caused a rise in the total acid-soluble and inorganic radioactive phosphorus of liver. In a further study (165) on rabbits the changes in the phosphates of the blood, muscle, and liver produced by insulin were studied by means of tracer experiments. Insulin caused an increase in the rate of disappearance of inorganic phosphate from the blood to become organically bound in blood, liver, and muscle.

Wertheimer (166) noted that when insulin was injected into either normal or adrenalectomized rats there was a transient deposition of glycogen in the adipose tissue. The effect was observed in both fed and fasted animals. Gregory *et al.* (167) found no evidence from a study on dogs that insulin or glucose alone or in combination had an effect upon the rate of metabolism of ethyl alcohol. In a study of mentally ill patients receiving insulin therapy it was found by Harris (168) that both insulin and carbohydrate administration lowered the level of glutamine-like substance in the blood serum. The effect of insulin was continued after the insulin hypoglycemia was alleviated by the administration of glucose.

Welsh (169) found that the responses of the isolated frog's heart and rectus abdominis muscle to acetylcholine were modified by the previous administration of insulin to the intact frog. At a temperature of 15 degrees C. the effect during the first twenty-four hours was to increase the sensitivity of the rectus muscle to acetylcholine and to decrease the degree of inhibition of the heart. Above 25 degrees C. the responses of the rectus muscle to acetylcholine six to twenty-four hours after insulin were subnormal and the degre of cardiac inhibition was increased.

Himwich *et al.* (170) concluded that due to lower cerebral metabolic requirements infant rats survived anoxia better than did adults. Hypoglycemia shortened the survival periods of both infant and adult rats during anoxia. The survival period of the anoxic infants, but not adults, was prolonged by the intravenous injection of glucose. Cats survived insulin hypoglycemia for longer

periods than rats but neurological damage was more readily produced in cats.

Opdyke (171) described a method for the biological assay of insulin based upon the blood sugar response of the fasting chick and observed (172) that previous injections of large doses of insulin greatly decreased the tolerance to glucose. Rosenbaum, DeKruif & Lavietes (173) noted that in normal men small doses of insulin were followed by a decrease in tolerance to glucose. Roberts & Samuels (174) found that adult male rats force-fed a high fat diet were less sensitive to the action of injected insulin than rats force-fed an isocaloric high carbohydrate diet. The decreased sensitivity was manifest as a markedly increased rate of recovery from insulin hypoglycemia. It was suggested that the cause may have been the higher level of liver glycogen in the fasted fat-fed animals.

Abrahamson (175) has presented evidence, principally argumentative, that hyperinsulinism is an etiologic factor in acute rheumatic fever. The evidence that rheumatic subjects have hyperinsulinism was based upon abnormal glucose tolerance curves in eleven patients having rheumatic fever. The assumption that the shape of a glucose tolerance curve is in itself an adequate criterion for the diagnosis for hyperinsulinism is, in the opinion of the reviewer, an unsound concept.

Nath (176) has reported on the isolation of a new anti-diabetic compound which was isolated from *Scoparia dulcis* Linn and was said to manifest its action in rats, dogs, and diabetic patients. The paper gave no data which would permit an evaluation of the substance or of the results obtained.

The Thyrotrophic Hormone and the Thyroid Gland

Means (177) has reviewed the new developments in thyroid physiology and Drill (178) has summarized the interrelations between thyroid function and vitamin metabolism.

Griesback & Purves (179) reported on the assay of thyrotrophic activity by the thyroid cell height response in guinea pigs. Smelser (180) has shown that the hypertrophy of orbital tissue of guinea pigs during experimental exophthalmos was due almost entirely to an increase in the water content of this tissue. Thyroidectomy caused no change from normal. Rawson, Graham & Riddell (181) found that tissue slices from the thyroids of patients with Graves'

disease inactivated twice as much thyrotrophic hormone as did normal thyroid tissue and concluded that the state of the "target organ" plays an important part in determining the response to a hormone. Galli-Mainini (182) observed a direct relationship between the activity of rat or guinea pig thyroid and the oxidase content of the tissue which was increased by the administration of thyrotrophic hormone or the implantation of anterior pituitary tissue and was decreased by hypophysectomy.

Goitrogenic substances.—Mixner, Reineke & Turner (183) demonstrated the goitrogenic effect of thiouracil and thiourea in the chick. Females exhibited greater responses than males. Williams *et al.* (184) studied the anatomic effects of thiouracil in the rat. The drug inhibited growth and tended to abolish the growth-stimulating effects of anterior pituitary growth hormone. The feeding of the drug to lactating mothers caused thyroid enlargement in the young. Gordon *et al.* (185) immersed frog larvae in a solution of thiourea and observed retardation of metamorphosis. The thyroids were atrophied rather than enlarged as in the mammal. Similarly, Hughes & Astwood (186) found that thiouracil inhibited the metamorphosis of tadpoles as normally induced by the injection of thyrotrophic hormone but not the metamorphosis induced by injections of thyroxine. Hughes (187) produced cretinism in rats by the administration of thiouracil daily from birth but it did not occur when thyroxine was given concurrently. The young of mothers given thiouracil showed thyroid hyperplasia at birth and subsequent retardation of development. Meyer *et al.* (188) demonstrated that thiouracil is relatively nontoxic in both normal and thyroidectomized rats. Higgins & Larson (189) have shown that Promizole (4, 2′-diaminophenyl-5′-thiazolesulfone) must be added to the list of drugs which are goitrogenic in the rat.

In a study of the respiration of tissues isolated from rats treated with thiouracil and with thyrotrophic hormone, Jandorf & Williams (190) found that the oxygen uptake of the thyroid was increased by both drugs and that the effect of the two together was greater than either alone. Liver and muscle showed an increased respiration when thyrotrophic hormone was administered but this rise was abolished by treatment with thiouracil. Thiouracil alone did not affect the oxygen uptake of liver and muscle. According to Williams *et al.* (191) the thyroid glands of guinea pigs which received thiouracil and thyrotrophic hormone were larger than the

ones which received either drug alone. Potassium iodide did not prevent thyroid enlargement. Thyrotrophic hormone caused a decrease in the amount of thiouracil stored in the thyroid but potassium iodide greatly increased the storage of this drug. Mackenzie & Mackenzie (192) observed that the administration of sulfaguanidine to young adult rats caused a sharp drop in metabolic rate, hyperplasia of the thyroid, and the appearance of thyroidectomy cells in the anterior pituitary. The intermittent feeding of sulfaguanidine to immature and adult rats failed to produce either a refractory or a hypersensitive state in respect to thyroid stimulation.

There is good agreement among investigators that the goitrogenic substances interfere with the formation of the thyroid hormone and that the hyperplasia of the gland is due to the compensatory stimulation of a hypoactive gland by the thyrotrophic hormone. Baumann, Metzger & Marine (193) found that thiourea caused thyroid hyperplasia in rabbits even when large quantities of iodine were given simultaneously. There was a rapid decrease in both thyroxine and nonthyroxine iodine in thyroid tissue. It was suggested that thiourea produced a functional thyrostasis of the thyroid cells. These authors emphasized that in the past there has been much opposition to the concept that cellular hyperactivity could coexist with hyposecretion as has now been proven in studies on the sulfonamides and thioureas. Such observations make it less difficult to accept the view that the hyperplastic thyroids seen in the early stages of endemic and experimental goiter produce an insufficient amount of hormone, while structurally similar goiters seen in Graves' disease produce an excess of hormone. In a study of young rats, Astwood & Bissell (194) noted that thiouracil caused a nearly complete disappearance of iodine from the thyroid glands in five days and a threefold increase in size in two weeks. Thyroxine caused a reduction in the size of glands of rats which were receiving thiouracil but did not permit a reaccumulation of iodine. Hypophysectomy resulted in regression in the size of the thyroids but did not alter their low iodine content. Thyrotrophic hormone caused thyroid hypertrophy but a relatively small loss of iodine.

Keston *et al.* (195) administered radioactive iodine to young and adult normal and thiourea-fed rats. Normal thyroid tissue was found to store considerable amounts of iodine, chiefly in or-

ganic form, but the thyroid tissue of the thiourea-fed rats failed to store any appreciable amounts. When pooled thyroid glands were incubated *in vitro* the addition of thiourea greatly lowered the iodine content of the tissue. Rawson *et al.* (196) found that the goitrogenic potency of thiouracil was greater than that of potassium thiocyanate in the rat. The thyroids of the thiouracil treated rats took up very little radioactive iodine but the thyroids of rats treated with potassium thiocyanate took up greater than normal amounts of iodine. It was suggested that thiouracil blocks the iodinization of the thyroglobulin molecule. Franklin, Lerner & Chaikoff (197) fed thiouracil to normal rats and noted that at the end of seven days the capacity of the thyroid to concentrate radioactive iodine and to convert it into thyroxine and diiodotyrosine was depressed. Normality was restored within two weeks following withdrawal of the drug. Franklin & Chaikoff (198) studied the *in vitro* effect of the sulfonamides on the conversion of radioactive iodine to thyroxine and diiodotyrosine in thyroid slices of sheep, cow, and dog. All of the sulfonamides, tested at a concentration of 10^{-3} *M*, inhibited the formation of the thyroid hormones but at this concentration sulfanilamide did not depress the iodine-concentrating capacity of the surviving thyroid slices. It was concluded that after the iodine has entered the gland it is the subsequent formation of the hormone that is inhibited by the sulfonamides. In a similar study of surviving slices of sheep thyroid, Franklin, Chaikoff & Lerner (199) found that thiourea, thiouracil, and allylthiourea each depressed the conversion of radioactive iodine to thyroxine and diiodotyrosine but none of these substances inhibited the iodine uptake by the thyroid tissue. Schachner, Franklin & Chaikoff (200) observed that cyanide and sulfide completely inhibited the formation of thyroxine and diiodotyrosine and depressed the accumulation of radioactive iodine by thyroid slices. Azide and sulfanilamide each inhibited the formation of the thyroid hormones almost completely but permitted large amounts of iodine to enter the tissue slices. From this and other studies it may be concluded that the ability of certain goitrogenic agents to inhibit the formation of the thyroid hormone may require a more complex explanation than the assumption that it prevents the tissue of the thyroid from taking up and concentrating iodine.

It has been shown (201, 202, 203) that the resistance of rats to

anoxia was increased by the production of thyroid insufficiency either by thyroidectomy or by the administration of the thioureas to intact rats.

There is uniform agreement among clinical investigators (204 to 213) that patients having thyrotoxicosis respond favorably to treatment with either thiourea or thiouracil but that longer periods of testing will be required to permit a full evaluation of the results. Rawson *et al.* (208) studied the action of thiouracil upon the thyroid gland in nineteen patients with Graves' disease. The lowering of the basal metabolic rate was similar to that of the iodine-response curve, both of which are similar to and may actually represent the thyroxine-decay curve. The decreased avidity of thyroid tissue for iodine was shown by the low values for radioactive iodine in thyroid tissue obtained by thyroidectomy in patients. An additional case of thiocyanate goiter in man has been reported (214).

Other studies on the metabolism of iodine.—Reineke & Turner (215) have reported improved methods for the isolation of crystalline thyroxine from iodinated casein and have described (216) the recovery of *l*-thyroxine from iodinated casein. Morton, Chaikoff & Rosenfeld (217) found that when thyroid slices were incubated *in vitro* the conversion of added iodide to thyroxine and diiodotyrosine was inhibited when the amount of inorganic iodide in the medium surrounding the thyroid slices exceeded a certain value.

Chapman, Higgins & Mann (218) fed young rats a low-iodine diet for ninety-five days prior to thyroidectomy. Half of the rats received additional iodine which did not influence the rate of growth in intact rats but there was a significant difference in growth and oxygen consumption of thyroidectomized rats with and without iodine, thereby confirming the earlier conclusions of these authors that iodine may be utilized by the rat in the absence of the thyroid gland. Chapman & Higgins (219) observed that the cytological changes in the anterior pituitary following thyroidectomy were intensified when the rats were restricted to a low intake of iodine.

Leblond (220) found that, fifteen hours after the injection of radioactive iodine in rats, the colloid in thyroids stimulated by thyrotrophic hormone contained increased amounts of iodine. Following hypophysectomy the amount of thyroid iodine was less than normal. Hamilton *et al.* (221) reported that the thyroids of

eight cases of hypothyroidism without goiters concentrated much less than normal amounts of orally administered iodine. The glands of two children having severe hypothyroidism with goiters took up relatively large amounts of iodine and by analysis were found to contain considerable quantities of both thyroxine and diiodotyrosine. It was suggested that the thyroid may have been able to form its hormone but not to release it. Frantz *et al.* (222) studied the function of metastases from a thyroid carcinoma by means of radioactive iodine. One metastasis in the femur showed a significant uptake of radioactive iodine and had the microscopic appearance of thyroid tissue.

Effects of the thyroid hormone.—Soffer *et al.* (223) attempted to identify the factors responsible for the elevation of bound magnesium in Graves' disease. The administration of thyroxine produced no appreciable change in the blood magnesium partition in normal dogs but thyrotrophic hormone caused an increase in the percentage of bound magnesium followed by a reduction below normal. Fink (224) administered thyroxine to dogs in doses sufficient to elevate the metabolic rate to hyperthyroid levels and observed a significant increase in the rate of jejunal secretion. Thyroidectomy did not affect the rate of jejunal secretion. Leblond & Hoff (225) reported that, in general, thyroidectomy reduced and graded doses of thyroxine increased the heart rate, body temperature, respiration, and oxygen consumption of rats. Dinitrophenol stimulated respiration, body temperature, and metabolic rate but affected heart rate only slightly. It was concluded that the effect of thyroxine on heart rate is not the consequence of general metabolic stimulation but is a direct effect on the heart. Winkler, Criscuolo & Levietes (226) found that the quantitative relationship between the basal metabolic rate and the dose of dried thyroid was linear in patients with myxedema. Winkler *et al.* (227) have shown that nonmyxedematous patients can tolerate large doses of dried thyroid without effect on the heart rate or basal metabolic rate. The subjects responded to the intravenous injection of thyroxine but larger doses were required by normal than by myxedematous subjects. It was suggested that normal subjects possess the ability to inactivate the thyroid hormone.

MacKay & Sherrill (228) found that renal function, as measured by the ratio between the urine urea excretion rate and the level of blood urea, was decreased in patients having hypothyroid-

ism and increased in patients having hyperthyroidism. Eiler, Althausen & Stockholm (229) investigated the effect of thyroxine on the maximum rate of absorption of glucose by the renal tubules of the dog. Thyroxine markedly increased the rate of glucose absorption. The hypothesis was advanced that thyroxine has an effect upon the rate of glucose absorption by activation of the system involved in the transfer of phosphate bond energy. Hare *et al.* (230) studied the diuretic action of dried thyroid in diabetes insipidus in the dog. It was concluded that thyroid increased glomerular filtration and diminished the effectiveness of pituitrin in controlling the renal tubular reabsorption of water.

Gordon & Heming (231) found that thyroxine or dried thyroid caused significant increases in the oxygen consumption of the liver, kidney, diaphragm, and heart of the rat. There was no effect on spleen, brain, or testis. Decreases in respiratory quotient were noted in hyperthyroid liver and diaphragm even in the presence of glucose and glycogen. It was concluded that the thyroid hormone is not a true catalyst in the oxidative enzyme system for, if such were the case, there would have been greater uniformity of effects among the various tissues. According to Lardy & Phillips (232) thyroxine in 1:75,000 dilution inhibited the respiration of bull spermatozoa and stimulated glycolysis

Effects of altered thyroid function.—According to Leblond & Gross (233) thyroparathyroidectomy in the adult rat caused a decrease in resistance to low temperatures. Chaikoff *et al.* (234) observed the development of cirrhosis in hypophysectomized-thyroidectomized dogs and a marked increase in the blood lipid and liver.

Williams & Kendall (235) studied two normal women who were given large doses of desiccated thyroid for 241 days. When adequate amounts of thiamine were given the basal metabolic rate was elevated but it decreased during thiamine restriction and was increased again when an adequate intake of thiamine was restored. Williams *et al.* (236) found that among a group of patients with thyrotoxicosis the levels of thiamine in the blood were lower than normal due to loss in the excreta and to the increased combustion of food.

Peters & Man (237) investigated the interrelations of serum lipids in patients with thyroid disease. Although the serum cholesterol was increased during thyroid insufficiency and decreased when treatment was given, normal concentrations of cholesterol

were found to coexist with both hyperthyroidism and hypothyroidism. The ratios of free to total cholesterol and of cholesterol to lipid phosphorus were not effected by thyroid disorders. There was no relation between the height of cholesterol and the level of neutral fat in the serum. Jailer *et al.* (238) studied seven thyroidectomized monkeys and failed to find any marked or consistent variations from normal. The serum cholesterol was increased in only one animal. A high dietary intake of cholesterol did not increase the serum cholesterol in thyroidectomized monkeys, thereby failing to reveal any latent disturbance in cholesterol metabolism (239).

The Parathyroid Glands

It has been definitely established that parathyroid extract has an effect upon the tissue of bone in nephrectomized rats. Ingalls, Donaldson & Albright (240) observed that parathyroid extract produced osteitis fibrosa in nephrectomized rats. Although nephrectomy alone produced some bone resorption the lesions were clearly distinguishable from those produced by parathyroid extract. Similarly, Stoerk (241) found that either a deficiency or an excess of parathyroid hormone affected the serum calcium of nephrectomized rats and that the injection of parathyroid hormone produced osteitis fibrosa in the absence of the kidneys to a greater extent than did nephrectomy alone.

Silberberg & Silberberg (242) reported that parathyroid hormone caused hypertrophy, calcification, and disintegration of growing epiphyseal cartilage without stimulating proliferation. There was later an increased resorption of cartilage and bone which caused a more rapid onset of epiphyseodiaphyseal union.

Tweedy & Campbell (243) found that parathyroid extract produced an increase in the amounts of phosphates in the liver and kidneys and a decrease in the femurs of rats.

Richter & Helfrick (244) noted that parathyroidectomized rats decreased their voluntary intake of dibasic sodium phosphate and that it was restored to normal by treatment with either parathyroid extract or with dihydrotachysterol.

The Metabolic Effects of the Sex Hormones

Mulligan (245) observed a loss of hair in male dogs following the prolonged administration of diethylstilbestrol. Mathews *et al.*

(246) found no effect of diethylstilbestrol upon blood pressure, heart rate, and respiration in the rat. Selkurt, Talbot & Houck (247, 248) demonstrated that estradiol benzoate increased the renal clearance of ascorbic acid in the dog by reducing tubular resorption. The plasma levels of ascorbic acid were decreased during treatment.

Ingle & Nezamis (249) tested progesterone, calciferol, posterior pituitary extracts, phenol, a urine extract, and water intoxication for a diabetogenic effect in partially depancreatized rats which consistently responded to diethylstilbestrol. No test substance, other than diethylstilbestrol, caused a response. Ingle (25) treated adrenalectomized-hypophysectomized-partially-depancreatized rats with a constant intake of subdiabetogenic amounts of anterior pituitary and adrenal cortical extracts and found that diethylstilbestrol exerted a diabetogenic action which was not mediated by pituitary or adrenal hormones. Davis & Jones (251) demonstrated a beneficial effect of diethylstilbestrol and of estradiol on the resistance of either normal or adrenalectomized rats to low pressures. Farmer (252) found that α-estradiol was without effect upon the sensitivity of serum sensitized female guinea pigs to anaphylactic shock. According to Winter & Thomson (253) castration did not affect muscle glycogen nor did the administration of testosterone or 11-desoxycorticosterone acetate alter the values for muscle glucogen in normal, adrenalectomized, or castrated rats.

Farbman (254) treated nine female patients having thyrotoxicosis with large doses of theelin without benefit but two cases of mild hyperthyroidism showed remissions.

Gardner & Pfeiffer (255) have reviewed the influence of estrogens and androgens on the skeletal system. There have been additional reports on the effect of estrogens in causing endosteal bone deposition in mice (256, 257), rats (258), and cocks and drakes (259). Segaloff & Cahill (256) concluded that dietary vitamin D does not play an important role in this mechanism. Lippman & Saunders (258) have contended that the effect of high doses of estrogens on bone is a part of the general depressing effect which estrogens have on body growth. The increased number and thickness of the trabeculae were regarded as secondary to the reduction of the water and organic constituents of bone.

Kenyon, Knowlton & Sandiford (260) have reviewed the ana-

bolic effects of androgens in man. Albright (75) has considered the evidence that the nitrogen balance in certain patients is related to the level of androgen production. Other reports have been published on the favorable metabolic effects of androgens in Addison's disease (261, 262), progressive muscular dystrophy in children (263), nephritis (264), and gastric carcinoma (265). Clark, Kochakian & Fox (266) observed that the mouse kidney lost a part of its ability oxidatively to deaminate *d*-alanine following castration. Treatment with testosterone propionate restored this activity to and above normal. Kochakian & Fox (267) found that the phosphatases of the liver and intestine were not affected by either a deficiency or excess of androgens in the rat. Castration was followed by a decrease in both the alkaline and acid phosphatases in the kidney. Testosterone propionate caused a decrease in the alkaline phosphatase and an increase in the acid phosphatase. Gaebler & Tarnowski (268) found that the nitrogen storage induced by testosterone propionate in normal bitches developed more slowly and was less marked than that following injections of growth hormone. Testosterone propionate induced a slight storage of nitrogen in depancreatized bitches on a constant intake of insulin. Upon the withdrawal of testosterone there was a marked glycosuria on the first day.

Miscellaneous

Reviews have been published on endocrines in general (269), the influence of the endocrine on the growth and aging of the skeleton (270), the role of the endocrines in the regulation of blood sugar (271), and the influence of the endocrine organs on intestinal absorption (272).

Bell & Cuthbertson (273) found that the administration of crude anterior pituitary extract, estradiol, and parathyroid extract to rats each produced heavier than normal bones but that the quality of the bone as shown by bending and twisting tests did not differ from normal. The feeding of thyroid produced a reduction in the soft tissue of bone but the quality of the bone did not deteriorate.

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HORMONES IN REPRODUCTION

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Even with the limitations on research imposed by the war, the literature concerned with the physiology of reproduction is extensive and it is impossible in the space allotted to review all aspects of the field. The papers included are chiefly those which appeared between January, 1943, and June, 1944. Inasmuch as certain aspects of the literature are given more emphasis than others some papers have been omitted intentionally and others no doubt have been overlooked. No particular effort has been made to consider the voluminous clinical literature.

A general review of the physiology of reproduction appeared in the 1943 volume of the *Annual Review of Physiology* (1) and in the 1944 volume consideration was given to the normal reproductive cycle, the physiology of the ovum and spermatozoan, the endocrine control of the mammary glands (2), and to the biology of semen (3). The development and function of the mammary gland has been the subject of a recent and comprehensive review (4), and the influence of sex hormones on the development of sex characters has been evaluated and summarized (5 to 8). Likewise the later research concerned with chemical aspects of gonadotrophic and lactogenic hormones has been discussed (9, 10). Among the numerous reviews available on the clinical use of hormones a series of three will be found in the *Journal of the American Medical Association* (11, 12, 13). Surveys of the literature on the chemistry and metabolism of steroidal substances have appeared (14 to 17).

Reproductive Cycles

During the past twenty-five years the study of reproduction in vertebrates has firmly established the hormonal nature of the controlling factors. The pituitary gland with its secretion of gonadotrophins is the dominant factor. In the female the ovum is of no demonstrable significance in the production of hormones by the ovary nor for menstruation (18). The essential aspects of the interrelationship of the nervous system, pituitary gland, and gonad in the control of reproductive processes are well recognized. These

relationships are being extended and clarified by the comparative and analytical study of reproductive cycles.

Mammals.—In the male rat it seems apparent that the testes secrete hormone as early as the tenth day of life and that during this period the seminiferous tubules are not dependent upon gonadotrophins (19). In the female the opening of the vagina occurs both before and after the beginning of the first estrus (20). The first ovulations take place between five and ten hours after the onset of the first heat period. The domestic rabbit is unique among mammals in having a type of follicular atrophy which is characterized by bleeding into the follicle (21).

The basic vascular pattern of ovarian follicles in the rat consists of a wreath of capillaries in the theca interna connected by branches from a wreath of arterioles and venules in the theca externa. After ovulation, capillaries from the theca interna grow into the corpus luteum and establish a typical pattern which is retained during the regression of the corpus luteum (22). Everett (23) has shown that improvement in the blood supply to the ovary of rats in persistent estrus induces a normal appearance in the interstitial cells. Intraocular endometrial transplants in the rabbit undergo vascular changes during pregnancy (24).

One aspect of a study of the differential cell division in the ovaries and genital tract of the rat near the time of ovulation indicates that uneven rates, or cessation of growth in the follicles of the next ovulation is the first sign of atresia (25). During proestrus and estrus in the mouse the mitotic activity of the epidermis varies directly with the number of follicles and the mitotic activity of the uterus (26). Maximal epithelial proliferation of the oviduct in the guinea pig occurs soon after ovulation (27). Unfertilized ova in the rat are washed out of the vagina near the end of heat and fragmenting ova are found in the uterus for as long as six days after ovulation (28). Early gestational changes in the whole vagina of the rat involve a proliferation of epithelial cells in a radial plane and mucification of the epithelium (29). Vaginal opening and descent of the testes of the cotton rat (*Sigmodon hispidus hispidus*) occur at about the same age as in the albino rat. Estrous cycles vary between seven and nine days throughout the year and gestation is approximately twenty-seven days in length (30). The spacing of ova in the uterus of the rabbit is controlled by the contractions of the myometrium, and these are in-

fluenced by the stage of the cycle (31). The cyclic changes in the vagina of the golden hamster (*Cricetus auratus*) are completed every four days during the year and the gestation period varies from fourteen to sixteen days. The animals breed throughout the year and the average size of the litter is ten (32).

In certain of the hibernating bats estrus is maintained from fall until ovulation occurs in spring. Although copulation takes place in the fall, supplemental matings occur during hibernation. Spermatozoa introduced into the female tract in the fall maintain their ability to fertilize eggs ovulated in the spring (33). In *Myotis lucifugus lucifugus* a single follicle which will ovulate in spring is found in the ovary in early October and does not undergo important changes until just before ovulation (34).

Delayed implantation of blastocysts and a very long gestation period are characteristic of certain of the mustelids such as the marten and the mink. Gestation in the marten can be shortened three to four months by artificially increasing the length of the day; less spectacular effects are found in the mink (35).

The antlers of the Virginia deer begin their annual renewal at the time when the testes and seminal vesicles are most inactive and become hardened when the gonads and seminal vesicles are growing. These changes are explained on the assumption that light initiates the cycle and that the pituitary stimulates the growth of the antlers in spring and activates the testes in summer. Hardening of the antlers is regulated by the testes alone or in conjunction with the pituitary. Shedding of the antlers in January is explained on the basis of a decline in androgen (36).

Ovulation in the cow occurs twenty-four to thirty-six hours after heat (37). Goats can be bred from the middle of September to the middle of December (38). A study of the reproductive cycles of the chimpanzee, baboon, rhesus monkey, and man shows that irregularities in the first cycles after the menarche are found in all. A seasonal amenorrhea is found in the chimpanzee and baboon during the winter and in the pubescent human female during the summer (39). The mean length of the vaginal cycles of a mature tarsier has been found to be 23.5 days. Cyclic activity is absent between late August and early November; no periodic appearance of blood is seen in the vaginal smear (40). A study of the changes in the vaginal smear and in the endometrium of women during the menstrual cycle shows that the endometrium is the better

criterion for judging the state of the ovaries (41). Rock & Hertig (42) have obtained evidence from the study of fertilized and non-fertilized ova which indicates that ovulation takes place in the human female approximately fourteen days before the first day of the next menstrual period. Comparison of the various methods used in determining the time of ovulation in women shows that the peak in gonadotrophin secretion which occurs in the mid-interval of the menstrual cycle is the most indicative of the exact time of ovulation (43).

Birds.—The growth rates of ova in the ovary of the pheasant, quail, chicken, and duck are essentially identical (44). The ovarian follicles of birds regress very rapidly after ovulation and are completely reabsorbed (44, 45). They are not regarded as functionally equivalent to the corpora lutea of mammals (45), although the removal of the ruptured follicle in the chicken postpones the laying of the egg from one to seven days (46). The nesting season of the English sparrow varies from March to September depending upon geographical location; usually two broods are raised (47). Although the testes of year-old male red-winged blackbirds (*Agelaius phoenicus*) come into active spermatogenesis in the spring as do adult males, most of the year-olds do not breed. Regression of the testes in the adult is correlated with the progression of the postnuptial molt (48). The ovary of the pheasant (*Phasianus colchicus torquatus*) begins to grow in March and thereafter increases rapidly in size. Increase in the size of the testes is found as early as February at which time sperm are found in the vasa deferentia (49). The bursa of Fabricius in the pheasant begins to involute during September and its regression is complete by late April (50). The presence of the bursa can be used to differentiate juvenile from adult pheasants (50), although incompletely involuted bursae have been found in a few adults (51). The rate of involution of the bursa can be increased markedly by the administration of testosterone propionate or of diethylstilbestrol to both castrated and normal male pheasants, but castration does not affect the rate of regression (52).

Avidin, the antibiotin factor responsible for dietary eggwhite injury, is found in the magnum of the oviduct of laying hens, but not in the uterus or isthmus. Avidin is not present in the atrophic magnum of the nonlaying hen (53, 54), but can be produced in immature chickens and nonlaying hens by stilbestrol followed by testosterone propionate, or by desoxycorticosterone acetate (55).

Modifying factors.—The importance of nonendocrine factors in initiating and modifying reproductive processes in certain species of birds and mammals is now well appreciated. Increasing the amount of light from the time of birth affects the development of ovarian follicles in the rat (56), but exposure of cotton rats to constant light from birth has little effect on the rate of development of the reproductive organs, yet constant darkness has a retarding effect (57). In doves, light is a factor which tends to restrict oviposition to daylight periods (58), and, in the starling, sperm formation is induced by light of wave lengths between approximately 0.58μ and 0.68μ (59). The yield of semen in chickens exposed to twelve hours of light daily is increased over that of those exposed to less than one hour daily; intensity of light, however, has very little or no effect (60). High environmental temperatures, humidity, or both, rather than ultraviolet light, seem to be responsible for the large size of the combs of Leghorn male chickens kept indoors (61).

The manner in which light modifies reproductive function suggests that a neuroendocrine control mechanism is operating. In rats an uninterrupted connection of the hypothalamus with the pars tuberalis and pars distalis is needed to insure a normal production of gonadotrophic hormones (62). Lesions in the hypothalamus and median eminence cause marked gonadal changes in some guinea pigs (63, 64, 65) and lesions in the anterior hypothalamus seem to interfere with the production of luteinizing hormone. Following such injuries ovulation cannot be evoked by injections of copper acetate or acetycholine (66). In normal rats, and in those with severed pituitary stalks, exposure to constant light induces continuous estrus and maintains follicles of ovulation size. Since ovulation and luteal function can be produced by sterile copulation (67), it seems that in the rat, and perhaps in the guinea pig (66), environmental stimuli produce their effects on the gonad by routes other than the pituitary (67).

Interest in aviation medicine has stimulated research on the effect of low atmospheric pressure on the function of the endocrine glands as related to reproduction. Sterility is common in horses, cattle, cats, and rabbits living at high altitudes (68, 69), and animals subjected to low atmospheric pressure show decreased fertility (70), absence of spermatogenesis (70, 71), and small testes (70 to 73); female rats show less marked changes in the repro-

ductive system than do male rats (73). Evidence indicates that the effect of discontinuous low pressure on the testes is probably direct and not by way of the pituitary gland, since the basophiles and the gonadotrophic activity of the pituitary are increased in rats and large doses of gonadotrophins do not repair the spermatogenic tissue (74).

Gonadotrophins

Depending upon their place of origin, the gonadotrophic substances[1] are commonly classified as pituitary or chorionic. The gonadotrophin in the serum of the pregnant mare (equine gonadotrophin) is not believed to be secreted by the chorion or pituitary gland but by specialized areas of the endometrium known as endometrial cups. The secretion from these cups contains more hormone than any other tissue of the pregnant mare (75). The gonad-controlling hormones of the anterior pituitary gland, judging from purified protein extracts, are thought to be three in number (9, 10, 76, 77). It is now well established that the follicle-stimulating hormone (FSH) causes growth of the ovarian follicle from the antrum to the preovulatory stage, and development of the seminiferous tubules of the testes. Preovulatory swelling, ovulation, and formation of the corpus luteum are dependent upon the action of the luteinizing hormone (LH) or the interstitial cell-stimulating hormone (ICSH) which is now recognized as being identical with LH (77). In both male and female, LH stimulates the interstitial cells of the gonad and in the male it also causes the production of androgen. LH augments the action of FSH when both are given subcutaneously, and the various conditions under which this effect can be produced have been discussed (78).

It has been shown that the maintenance of the corpus luteum depends upon a third pituitary substance called luteotrophin (79) which, however, may be the lactogenic hormone, since purified lactogen will maintain the secretory function of corpora lutea (80, 81). Luteotrophic activity is also present in extracts of rat placentae (82).

According to Smelser (83) gonadotrophic hormone is found in greater concentration in the basophilic central zone of beef an-

[1] Corner (74) has recently discussed the reasons for using the terms gonadotrophin and gonadotrophic as noun and adjective when referring to a substance and to the action of a substance that stimulates the gonads.

terior pituitary gland than in the acidophilic and chromophobic cortical region. A simple procedure has been developed for obtaining a gonadotrophic preparation containing FSH and LH and free from the lactogenic hormone. The latter can be recovered by extraction with aqueous alcohol (84).

A new method (85) for the preparation and purification of chorionic gonadotrophin from pregnancy urine has been described. It involves the use of chromatographic adsorption of the active substance on permutit and the recovery of the gonadotrophin by alcoholic ammonium acetate. The purest preparations have a potency of 8500 I.U. per mg.

It has been shown that absorption of many of the biologically active steroids can be varied by changes in the method of administration. One of the most satisfactory procedures for prolonging absorption is by subcutaneous implantation of pellets (86, 87). The general success of this method has led to disappointment in its use with chorionic gonadotrophin which is found to be absorbed rapidly even when 90 per cent cholesterol is added as excipient. Pituitary gonadotrophin is more slowly absorbed, and therefore more efficient, when administered with excipient than when injected (88). More effective clinical use of gonadotrophins may result from the use of the implantation technique (89). Augmentation of the action of pituitary gonadotrophic extracts in male (90) and female rats (91, 92) has also been produced by the injection of a mixture of gonadotrophin and hemin.

The action of gonadotrophins is affected by many factors and one of the more important is the age of the animal being injected. The first response of the testis and ovary of rats to equine gonadotrophin is obtained between birth and six days of age for the testis, and between four and ten days of age for the ovary (93). Treatment of pouch-young and juvenile opossums with equine gonadotrophin shows that the testes can secrete androgen as early as day seventy, and that the ovaries produce estrogen by day one hundred. Embryonic egg nests are converted into primordial follicles before day one hundred (94). Leathem (95) has shown that the luteinizing action of equine gonadotrophin in hypophysectomized immature rats is dependent upon the route of administration as the greatest increase in seminal vesicle weight is obtained by daily intraperitoneal injections.

The ovaries of immature rabbits do not respond to chorionic

gonadotrophin, but growth of follicles can be produced if the gonadotrophin is given after the rabbits have been treated with thyroxine (96). The response of the ovaries of rats to pituitary, chorionic, and equine gonadotrophin is enhanced by partial nephrectomy; the augmented response to chorionic gonadotrophin is greater than to the other gonadotrophins. It is suggested that the failure of chorionic gonadotrophin to increase ovarian weight in proportion to increase in dosage is due to a low renal threshold for this hormone (97). The gonadotrophins of male rat pituitary glands are more effective than are those of the female in increasing the weight of the ovaries of rats. The effect of one-half of a male pituitary is augmented by the simultaneous injection of three female glands which by themselves have very little effect; the action of pregnant mare serum (PMS) is augmented by both male and female rat pituitaries (98). Superovulation, as well as ovulation of normal numbers of ova, can be induced by the injection of gonadotrophins into intact immature and hypophysectomized rats (99, 100), rabbits (101, 102), calves (103), cows (103, 104), and ewes (105, 106). In sheep the reproductive state of the animal, at the time of artificial maturation of follicles and ova, influences the fertility of the eggs ovulated. This is indicated by the greater fertility of ewes treated with FSH and unfractionated extracts, or with FSH and LH, during the follicular phase of the estrous cycle than is obtained in ewes injected during the luteal or anestrous phase (105). Superfecundation is found in the early stages of pregnancy but usually an excessive number of young are not born (101 to 104, 106), although several twin and triplet births have been reported for cattle treated with gonadotrophins (104). It has been suggested that the high embryonic mortality may be the result of an inadequate uterine environment due to a direct or an indirect effect of the gonadotrophic treatment, or to abnormalities induced in the ova by the rapid maturation of follicles (106). Successful attempts to prolong the life of embryos in superfecundated juvenile and adult rabbits by progesterone, or by a combination of progesterone and estrogen, indicate that embryonic death is due to a uterine deficiency rather than to defects in the ova, although the possibility of the latter has not been excluded. This idea is also supported by the finding that artificially matured and ovulated ova survive as well after transplantation into the uteri of normal host females as do naturally ovulated ova from normal females (102).

The administration of FSH extracts subcutaneously to ewes, followed by LH intravenously, in the last days of the estrous cycle lengthens the period of estrus approximately 50 per cent (107). This treatment does not affect either the time of the beginning or end of estrus in ewes (107), or in cows (103); it does not cause estrus when administered late in the first week of the cycle, nor in most ewes when given during anestrus (107). Estrous behavior is induced only rarely in anestrous ewes given a single dose of PMS, but two doses given sixteen days apart incite estrus in most ewes; ovulation results from one or more injections of PMS (108).

In cats one large injection of PMS causes large multilocular follicular cysts which regress, persist as simple retention cysts, or form corpora lutea (109). Cystic ovaries and associated nymphomania in cattle have been treated successfully by the intravenous injection of an unfractionated sheep pituitary extract (110). In the majority of the animals the symptoms of nymphomania disappeared after one injection, but in several, two or three injections were required. Often the symptoms of nymphomania subside within twenty-four hours after the administration of gonadotrophin. Corpora lutea are formed within thirty-one days of treatment and normal estrus occurs in most of the treated cows. Of fifty-three animals which were bred following a single injection, thirty-six became pregnant.

Attempts by Hartman (111) to produce ovulation in the ovaries of adult rhesus monkeys by the use of gonadotrophins have not been encouraging although results of experiments done with an additional series of thirty monkeys show that ovulation was induced in six animals (112). PMS preparations were responsible for three cases of ovulation, but were without effect in five and led to overstimulation in ten others. FSH preparations caused ovulation in three other monkeys, but were ineffective or produced overstimulation in others. Hartman concludes that in the present stage of our knowledge it is not possible to predict what effect gonadotrophins will have on the ovaries of adult monkeys (112) and critical evaluations of the action of gonadotrophins on the ovaries (12, 113, 114) and testes (115, 116, 117) of the human being indicate that the factors necessary for physiological stimulation are poorly understood.

It has been well established that the type of gonadotrophic activity found in the urine of castrated and menopausal women is

largely follicle-stimulating and that it is secreted by the pituitary gland. Jones & Bucher (118) have developed a method for concentrating this gonadotrophin in such a way that destruction or change in the active substance is minimized. The various fractions they obtained from the urine of menopausal and menstruating women, and from normal men, were injected into hypophysectomized animals. The results show that FSH is found in the urine of all three types and is best precipitated at pH 6.8 by a saturated solution of ammonium sulphate. No evidence of adrenotrophic, thyrotrophic, or LH activity was obtained. Excretion of increased quantities of gonadotrophin in the urine of human females occurs within six days after castration and menopausal levels are found by the tenth day (119). That the pituitary gland is still capable of secreting supranormal quantities of gonadotrophin forty-four to fifty-seven years after removal of the testes is demonstrated by the large amounts of it found in the urine of eunuchs who had been castrated between eight and twelve years of age (120). The gonadotrophin in the urine of castrated women is augmented by a dialyzable substance found in the same urine; this indicates that assays of alcohol-precipitates of such undialyzed urine give values which are too high (121).

Gonadotrophins of various kinds produce progonadotrophic as well as antigonadotrophic substances in experimental animals (122) and in man (123). The effectiveness of antigonadotrophic substances in preventing the action of gonadotrophins is influenced by the purity and source of the gonadotrophic preparations and whether the antisubstance is mixed with the gonadotrophin before injection (124). In general, the antigonadotrophic substances are not specific and can inhibit the action of endogenous pituitary gonadotrophin (19). No attempt will be made here to review or correlate the literature dealing with this subject and the reader is referred to reviews which have appeared recently (1, 10, 125).

Sex Hormones

Estrogens.—The growing follicle is probably the main source of estrogen secreted by the ovary, but the specific tissue responsible for its production remains to be determined. Histochemical methods applied to the ovary of the rat show that the typical reactions of steroid compounds are given by the theca interna, interstitial

cells, and corpora lutea, but not by the granulosa (126). Application of the histochemical method to the study of certain neoplasms (127, 128) of the human ovary should yield additional information which will be of value in determining the site of origin of sex steroids. That the problem is not a simple one is shown by the recent finding (129, 130) that cells which are morphologically and functionally like those of the adrenal cortex develop in the ovaries of adrenalectomized ground squirrels (*Citellus tridecemlineatus*).

It has been suggested by Bullough (131) that estrogen, in addition to its growth promoting effect on the female accessory sexual organs, acts directly on the ovary causing cell division in the germinal epithelium (132), in growing follicles, and corpora lutea (133). The indications are that low concentrations of estrogen stimulate growth in the reproductive tract of the female, but that high concentrations are necessary to cause active mitosis in ovarian tissue. His theory assumes that high levels of estrogen depress the gonad-stimulating function of the pituitary and thus diminish the estrogen level in ovarian tissue and inhibit mitosis of ovarian cells (133).

It is well known that estrogen has important effects on the secretion of pituitary gonadotrophins and in the female it is considered to be an important factor in regulating ovarian function. It is generally agreed that following removal of the ovaries there is an increase in the amount of gonadotrophin and in both the number and size of the basophiles of the anterior pituitary gland. This condition, together with an increase in the amount of gonadotrophin in the blood, can be produced in rats by the injection of anti-gonadotrophic rabbit serum (134). Castration of the adult opossum causes an increase in the number and size of the basophiles and a similar condition is seen in the pituitaries of the young opossum before the gonads begin to function in an endocrine capacity (135). In a detailed study of the effect of advancing age on the pituitary and the ovaries of rats, a condition somewhat similar to that in the young opossum is seen in the basophiles of month-old animals (136). Such studies provide the kind of data which investigators in the past have used, in part, to support the theory that gonadotrophin is produced by the basophile cells of the anterior pituitary.

In the human female large quantities of gonadotrophins, such as are found during the menopause, are excreted in the urine following ovariectomy (119, 137) and it has been suggested that this

increase is not due to hypophyseal hypersecretion, but to nonutilization of the hormone by the ovaries (137, 138). Excess gonadotrophic excretion is not prevented in ovariectomized women by daily doses of 0.5 mg. of diethylstilbestrol although the menopausal symptoms are alleviated. Doses of 1 mg. per day cause some decrease below the menopausal level and doses of 5.0 mg. completely prevent the excretion of gonadotrophins (119, 137). In rats a dose of estrogen calculated to be five to seven times that secreted by the rat's ovaries largely prevents the increase in pituitary gonadotrophin which follows ovariectomy (139). These results demonstrate that estrogen, in large doses at least, suppresses the production of hypophyseal gonadotrophins. It has also been shown in the ovariectomized rat that relatively large doses of estrogens are necessary to produce the increase in mitotic activity seen in the pituitary during estrus (140); similar results have been reported for the mouse (141).

According to Baker & Everett (142) estrogen has a differential effect on the secretory cells of the anterior pituitary. They found that diethystilbestrol, when injected into immature female rats in daily doses ranging from 0.05 to 4.0 μg. for four to seven days, causes an increase in both the number and granulation of the acidophiles, but a decrease in the number and a degranulation of the basophiles. Injection of the smaller dose for fourteen days, however, causes a slight reduction in the number of acidophiles. These authors conclude that estrogen stimulates the acidophiles of the pituitary and they summarize the evidence which indicates that the acidophiles are the source of the luteinizing and the luteotrophic hormones.

Recently Heller and others (137) have obtained results which indicate that small doses of estrogen enhance the gonadotrophic activity in the urine of castrated women. That this augmented activity might be due to an increase in luteinizing hormone is indicated by the diffuse luteinization of the ovaries of the test rats. Since it has been shown that estrogen causes hyperplasia of the chromophile cells of the pituitary in both human males and females (143), it may well be that the acidophiles are the source of the luteinizing hormone produced by the human pituitary.

Considerable attention is being devoted to the comparative physiology and chemistry of both the natural and the artificial estrogens. It is not possible in this review to consider all of the

literature concerned with the study of the ever-growing list of estrogenic compounds. Among others, a new active estrogenic substance, 2:4-di-(parahydroxyphenyl)-3-ethyl hexane, known as "octofollin" has been synthesized and its physiological effects studied (144 to 148). It, like diethylstilbestrol and hexestrol, seems to have about the same physiological action as natural estrogens.

Inasmuch as rate of absorption is important in determining the hormonal effectiveness of estrogens, various methods have been developed for slowing up this process. Implantation of pellets is probably the most satisfactory method as both absorption (86) and action are prolonged (87, 149). Cast pellets of steroid hormones do not disintegrate after implantation and are absorbed at a predictable rate (150) and at about the same rate as tablets made by compression (151). Protein material is deposited throughout the tablets, but only superficially in fused pellets (151).

The effects of estrone, estradiol benzoate, progesterone, and testosterone are prolonged by adsorption on carbon, but that of diethylstilbestrol is not sustained (152). Feminization of the ventral feathers of Brown Leghorn capons has been used to measure the rate of the absorption of esters of estrone and estradiol (153). Cutaneous application has proven to be a simple and effective way to administer ethinyl estradiol (154). On the other hand oral administration seems to be the method preferred in clinics, judging from reports on the use of ethinyl estradiol (155), diethylstilbestrol (156, 157, 158), hexestrol (157 to 160), and conjugated estrogens from pregnant mare's urine (161 to 168) in the treatment of various gynecological conditions. Steroid hormones are absorbed from the oral mucosa (169, 170, 171), and estrogen is as effective by sublingual as by intramuscular administration (169).

It has been postulated that certain artificial estrogenic compounds are themselves inert, but are wholly or partly metabolized to active compounds by the tissues (172 to 175). The term proestrogen has been proposed for such a compound (172). Adaptation to one action of a steroidal compound, such as estrogen, may occur while its other effects remain stationary, or show a cumulative increase during treatment (176). It has been suggested that the transitory vaginal cornification induced by steroids is due to their folliculoid activity (177). The vaginal smear has been shown to be of value in determining the effectiveness of estrogen therapy in the human female (178, 179). The accuracy of the vaginal smear

method for assaying estrogen in animals (180) and the variables affecting such a method have been determined (181, 182). Pellets made from the desiccated blood of young women do not give any evidence of estrogenic activity when applied intravaginally in castrated rats (183). The vascular response of the uterus of the castrated guinea pig can also be used for the assay of estrogen (184).

Studies of intraocular implants of endometrium indicate that the growth of the uterine mucosa depends on the level of estrogen in the blood rather than on the amount of endometrium (185). The effect of estrogen on the uterine epithelium has been described (186) and it is claimed that estradiol does not have any effect on the acetylcholine content of the uterus of the castrated rabbit (187). Although diethylstilbestrol is bactericidal and bacteriostatic (188), mice develop uterine infections following its injection or that of triphenylethylene or estradiol benzoate (189). Infections of the ovaries and reproductive tract are found after the injection of estrogens into rats (190).

Lipschütz and others have published a series of papers which report: (*a*) the fibromatogenic activity of estrogens (191 to 194); (*b*) the relatively high antifibromatogenic strength of progesterone (195, 196, 197) as compared to other steroids (198, 199); (*c*) the chemical structure of steroid substances as related to their antifibromatogenic activity (200, 201); and (*d*) the inactivation of antifibromatogenic steroids by the liver (202). The results of these studies form the basis for an understanding of the endocrine factors involved in antitumoral defense (203).

The action of estrogen is not limited to the tissues of the reproductive tract, and of the various other effects which are produced only a few will be mentioned. Estrogen is responsible for the development of color in the sexual skin and tail areas of the rhesus monkey and a method has been described for recording the color changes (204). It produces melanosis of the vagina in rats treated with organic bismuth compounds (205); it has important effects on the ossification of bones (206 to 211); it produces urinary tract calculi in male rats (212); it has been reported both to be without effect on blood pressure (213) and to increase it in normal rats (214); it decreases blood pressure in hypophysectomized rats (214); it causes a loss of hair in male dogs (215), and rats (216); it increases micturition volume in female rats to levels found during pregnancy and following parturition (217); it stimulates nor-

mal growth in the atrophic human buccal mucosa (218); it activates some neural mechanism so that copper salts can induce ovulation and pseudopregnancy in the anestrous rabbit, and pseudopregnancy in rats which are in met- or diestrus (219); it produces marked changes in the pituitary gland and related nuclei of the hypothalamus (220); and since it has a caponizing effect it has been recommended for use in fattening chickens (221).

Progesterone.—It has been well established that the corpus luteum is the source of the progesterone produced by the ovary, but other substances not secreted by the ovary have progesterone-like activity. Among the forty-five substances tested by Selye & Masson (222) for luteoid activity, fifteen have been found to have progesterone-like action. Of the fifteen, progesterone, ethinyl-testosterone, desoxycorticosterone acetate, and vinyl-testosterone are four of the most potent and they are listed here in the order of increasing activity. The progesterone-like properties of the steroid desoxycorticosterone acetate is also demonstrated by results which show that deciduoma can be induced by its injection (223). A quantitative comparison of the luteoid activity of testosterone propionate with that of progesterone shows that this androgen has weak progesterone-like action on the reproductive tract of the female rhesus monkey (224). Progesterone possesses andromimetic activity (225) and, in common with desoxycorticosterone acetate and certain other steroids, it causes compensatory atrophy of the adrenals (226).

That progesterone may have important regulating effects upon the secretion of pituitary gonadotrophin is indicated by the observation that it is effective in preventing the development of castration changes in the pituitary gland of rats (227). Evidence is also available (228) which indicates that in the normal rat progesterone accelerates the secretion of luteinizing hormone and that in rats in persistent estrus a single injection often causes atresia of the large follicles and interruption of the condition of continuous estrus; a second injection during the induced diestrus causes formation of corpora lutea (229).

The importance of the corpus luteum for the maintenance of pregnancy is shown by the fact that following ovariectomy, in most animals, the duration of pregnancy is shortened. It has been reported that the period is approximately forty-eight hours for the rat, but recent studies by Zeiner (230) show that this can be pro-

longed to an average period of eighty hours by improved operative techniques. Pregnancy is sustained beyond the eighty-hour period by the injection of progesterone followed by estrogen. In hypophysectomized and ovariectomized pregnant rats a combination of progesterone and estrogen makes it possible for pregnancy to be maintained for the normal period and it is suggested that the pituitary is necessary for the production of progesterone and estrogen during the first half of pregnancy (231). Prolongation of pregnancy during lactation occurs in some rodents, such as mice, and can be further prolonged by the administration of progesterone or by the injection of lactogenic hormone which, due to its luteotrophic action, prolongs the secretion of progesterone (232). Atkinson (233) has shown that the survival period of deciduomata in pseudopregnant rats can be extended to a maximum of ten days by the injection of progesterone. These results indicate that deciduomata have an inherent life-span—dependent, however, upon progesterone. A possible functional interrelationship between the pituitary, corpus luteum, metrial glands, and deciduoma is suggested by the results which show that deciduomata cause a prolongation of pseudopregnancy to the period of normal pregnancy in the rat (234). The results of experiments here discussed provide the basis, in part, for the use of progesterone in the treatment of threatened and habitual abortion in women and a recent clinical report has summarized the results of this and other types of therapy (235).

The use of progesterone therapy in the human being would be much simplified if progesterone could be administered orally, but the evidence shows that it is not effective after ingestion. Data have been obtained, however, which signify that progesterone and anhydro-hydroxy-progesterone are effective in large doses when administered sublingually to women; the effectiveness was determined by the precipitation of menstruation (170). In experiments done with monkeys and rabbits it has been found that progesterone produces variable results when sublingual administration is used; the quantity required was estimated to be four or five times the intramuscular dose (169).

Relaxin.—In 1926 it was shown (236) that relaxation of the ligaments of the symphysis pubis of the pregnant guinea pig is under the hormonal control of a specific substance called relaxin which is found in the blood of some pregnant animals, in the cor-

pora lutea of the sow, and in the placentae of rabbits (237, 238). Other workers, however, found that relaxation of the ligaments could be produced by estrogens (239) and by combinations of estrogen and progesterone (240). These data raised doubt in the minds of some as to the existence of a specific hormone, regardless of the fact that the effect on the ligaments occurs within six to eight hours after injection of relaxin, as compared to a matter of days for estrogen, or for a combination of estrogen and progesterone.

During 1944 Hisaw and his co-workers have reported new data which provide the basis for a more complete understanding of the role of endocrine factors in the relaxation of the pubic ligaments. A new and simple procedure for preparing relaxin from the corpora lutea of the sow is described. The product obtained contains one guinea pig unit per mg. of dry weight; it is not steroid in nature and has no estrogenic or progesterone-like activity (241). Castrated guinea pigs which have been sensitized with estradiol are used to assay relaxin and by this means it has been found in the blood of pregnant rabbits as early as the third day after mating. It increases to maximum quantities at approximately the twenty-fourth day of pregnancy and decreases markedly immediately after parturition. Relaxin (242) is found also in the urine of pregnant rabbits as early as the fifth day and increases with the progress of pregnancy.

Neither progesterone nor estradiol causes relaxation of the pelvis in castrated hysterectomized guinea pigs, but relaxin does. These results, although not in agreement with those of another investigator (243), show that the uterus is necessary for the relaxation produced by estrogen or progesterone and for the appearance of relaxin in the blood; and they strongly suggest that the uterus, under the influence of estrogen or progesterone, plays an important part in the production of relaxin in the guinea pig. Further evidence is provided by the fact that both progesterone and estradiol cause relaxin to appear in the blood of castrated rabbits, but not in rabbits which are castrated and hysterectomized, nor in castrated males. Thus, the seemingly conflicting data are brought into agreement and the conclusion seems warranted that relaxin is a specific hormone which does not have the same chemical or physiological properties as are possessed by estrogen or progesterone (244).

Androgens.—It is the generally accepted view that the interstitial cells of the testes of mammals are the source of androgen. Additional evidence for this concept (245) is found in the recent studies which show that histochemical reactions which indicate the presence of steroid substances are obtained in the interstitial cells, but not in the seminiferous tubules.

The androgen content of the testes of bulls increases markedly between two and five years of age together with extensive vacuolation and increase in the size and number of Leydig cells. From the fifth to the fifteenth year the androgen content decreases, accompanied by loss of vacuolation and diminution in size of the cells (246). In the English sparrow androgen is produced during the normal sex cycle, and following stimulation of the testes by light or by small doses of gonadotrophins, but Leydig cells are not found. This suggests that in birds androgen may originate in the germinal epithelium. Injection of large amounts of equine (PMS) or pituitary gonadotrophins, however, stimulates the transformation of connective tissue cells into Leydig cells and androgen is secreted in the absence of an active germinal epithelium (247). The source of androgen produced by the ovary under certain conditions is probably the cells of the theca interna since in the human female (248, 249), and in female rats bearing ovarian grafts (250), theca cell hypertrophy and hyperplasia are correlated with androgen production.

A method for assaying androgen has been described, which is based on the production of pigment in the bill of castrated male English sparrows. As little as 0.063 μg. of testosterone can be detected by this method. Estradiol benzoate does not alter the response to testosterone (251). Another modification of the comb growth method for the assay of androgen has been described (252). Likewise data of value, for those using the comb growth method of androgen assay, will be found in a paper describing the results obtained with different linear measurements of the size of the comb in White Leghorn cockerels (253). Recently, Parkes & Emmens (254) have summarized our knowledge concerning the effect of pure androgens and estrogens on the reproductive organs and secondary sex characters of birds.

The influence of androgens and estrogens on the development of the undifferentiated gonads and reproductive tissues of vertebrates has been discussed and summarized in several recent reviews (5, 6, 7). The response to steroidal hormones is variable and

often unpredictable. In mammals no permanent effect on the gonads is evident and androgens fail to modify ovarian development. It is evident that the administration of androgens to sexually undifferentiated mammals, such as the opossum, do not duplicate the conditions found in the free martin or else a species factor is involved (255).

Sexual development in *Rana pipiens* is profoundly affected by pregneninolone, as 100 per cent of the sexually undifferentiated larvae become males when treated (256). Tendencies toward sex reversal are found in the testes of *Amblystoma punctatum* fed pregneninolone (257); marked stimulation of the Müllerian ducts has been induced in both *Rana pipiens* (256) and *Amblystoma punctatum* (257) by pregneninolone. Pseudohermaphroditism has been induced in the female young of the monkey by the administration of androgen to the pregnant mother (258).

Androgen has both stimulatory and inhibitory effects on the gonads depending upon the species and the dose administered. Testosterone propionate (259) can cause full spermatogenesis and the production of large quantities of spermatozoa in the post-spawning testes of the minnow (*Phoxinus laevis* L.), and it is suggested that spermatogenesis and oögenesis are controlled by androgen and estrogen respectively. Hypertrophy of the gonad in the female English sparrow can be produced by testosterone propionate. These effects are explained on the basis that androgen stimulates the pituitary to secrete gonadotrophic hormones (260). Testosterone propionate does not induce the formation of spermatozoa in rats hypophysectomized at twenty-seven days of age, although spermatids are formed; continued treatment results in damage to the seminiferous tubules (261). Pregnenolone, although without effect on the seminal vesicles of rats, maintains spermatogenesis in hypophysectomized adult rats. However, pregneninolone, which has androgenic activity, fails to maintain spermatogenesis (262). In the ground squirrel (*Citellus tridecemlineatus*) large doses of androgens cause severe damage to the interstitial cells of the testes, but not to the germinal epithelium (263). Likewise compounds having androgenic properties cause involution of the interstitial cells of the testes of the fowl (226). A mixture of androstenediol and estradiol cause more marked atrophy of the testes in the rat when given in small than in large doses (264).

Androgens prevent the luteinization of the ovary of the rat at any age (265) and when administered to male rats of different ages

between birth and twenty-eight days of age they severely affect testicular function subsequently as determined by low libido, small testes, and atrophic prostates and seminal vesicles (266). In male rats reversal of pituitary castration changes are obtained with large doses of androgens, but not with small ones (267). Hellbaum & Greep (268) conclude that in the castrated male rat androgen brings about the release of the luteinizing factor from the pituitary, and suppresses the liberation of follicle-stimulating hormone. Testosterone propionate injections initiated on the day of birth arrest follicular development and cause a partial change of follicles into seminiferous tubule-like structures in the rat (265). Androgens, however, hasten the recovery of rats from the damaging effect of estrogen on the testes (269) and Weichert & Hale (270) find that they completely prevent the squamous metaplasia produced in the epithelium of the accessory organs of the male rat by diethylstilbestrol. They suggest that as the male rat grows older it loses its capacity to respond to estrogens because of the increase in the secretion of androgen.

Further investigation has been made of the role played by androgens in the descent of the testes and the present status of the problem has been presented recently in a comprehensive review (271). It is generally agreed that descent is controlled by the interaction of hormonal and mechanical factors. The extent to which the mechanical factors are dependent upon the action of hormones has been the subject of several recent papers. In the ground squirrel androgen causes the inguinal bursa to increase in weight even when the bursa has been deprived of its gubernaculum, epididymis, and testis (272). It seems probable that the gubernaculum and the epididymis in the earlier stages of descent are mechanical factors which, in conjunction with androgen, cause the bursa to enlarge enough to receive the testis (273). Experiments done with rats (274, 275) and monkeys (275), in which "artificial testes" were used, provide additional evidence which supports the concept that the size of bursa and scrotum are determined by a hormonal factor (androgen) plus the mechanical action of the contents of the inguinal bursa (271, 273, 276); the action of androgen is extragonadal as it controls growth and contractility of the testicular adnexa (275, 277). The growth of the testis is a mechanical factor which, like the production of androgen, is controlled by gonadotrophins. Testicular growth, however, is not a major factor in the descent, since "artificial testes" which cannot grow will descend under the

influence of androgen (275). The gubernaculum does not seem to be necessary for the final stages of descent and it has been suggested that at this time it serves to guide the testis into the bursa (273). It is questionable whether the gubernaculum can exert enough traction to pull the testis into the scrotum (271, 278).

Androgens have been widely used in the treatment of various dysfunctions of the testes and other diseases of the genitourinary system (13, 279). No attempt is made here to review the clinical literature in this field, but mention will be made of a few of the papers. Recent studies in the use of testosterone indicate that the best therapeutic effects are seen when it is used as replacement therapy in hypofunction of the testes (280). The use of androgens for dysfunction of the seminiferous epithelium (281, 282), in male eunuchoids (283), and in the treatment of Simmond's disease (284), have been reported. Hoskins (285) has discussed the relation of androgens to kidney function in the human being and it has been shown that testosterone propionate increases the tonus of the urinary bladder in men and women (286). Additional evidence has been obtained which shows that testosterone propionate has a weak progesterone-like action on the reproductive tract of the female monkey (224) and it has been used for the treatment of endometriosis (287, 288) and excessive uterine bleeding (289).

Mention should be made of a few of the miscellaneous effects produced by androgen. In the fowl it increases the number of erythrocytes (290, 291) and inhibits the development of the uropygial gland and the bursa of Fabricius (292), but in the pheasant it increases the rate of involution of the bursa (52). It exerts anabolic effects on the extragonadal tissues (293) and induces and maintains a dimorphic pigmentation in the skin of the male golden hamster (*Cricetus auratus*) (294). In the rat, it causes involution of the glomerulosa of the adrenal cortex (295) and, in mice, disappearance of the X-zone of the cortex (296).

Numerous papers concerned with the metabolism of sex hormones continue to be published and the reader is referred to recent reviews which discuss this subject (14 to 17).

Mammary Gland

The hormonal regulation of the growth and secretion of the mammary gland has been discussed extensively in recent reviews (1, 2, 4, 297). Mixner & Turner have summarized the literature concerned with the question of whether estrogen and progesterone

act directly or indirectly on the mammary gland. In addition, they have reported the results of experiments concerned with lobule-alveolar growth in mice and goats and the assay of the lobule-alveolar factor (297). In 1939 these same workers summarized the results of their experiments relating to duct growth of the mammary gland (298). The evidence for and against the existence of a duct growth factor (Mammogen I) and a lobule-alveolar growth factor (Mammogen II) has been presented together with a description of the isolation, the physicochemical properties, and assay of the pure lactogenic hormone (299). Recent results obtained by Turner and his co-workers (300) indicate that the hypophyseal duct growth factor is protein, rather than lipid, in nature.

The growth of the gland until the time of sexual maturity closely follows that of the body. Hormonal factors begin to act with the onset of sexual maturity and estrogens cause the pituitary gland to secrete an increased amount of the mammogenic duct substance. Estrogen directly causes growth of the teat and the stromal tissue of the gland and thus aids the direct action of the pituitary duct and lobule-alveolar factors. Progesterone induces lobule-alveolar growth, probably by causing the secretion of a mammogenic lobule-alveolar growth substance, which is not the same as lactogen, thyrotrophin, gonadotrophin, or growth hormone (297).

Progesterone, pregneninolone, desoxycorticosterone, dehydroandrosterone, diethylstilbestrol, acetoxy-pregnenolone, and methyl-testosterone rank in the order named in their power to cause lobule-alveolar growth in mice and, correspondingly, in their relative potency in producing progestational proliferation in the endometrium (297). Desoxycorticosterone is said to be without effect in hypophysectomized rats (301).

Lyons has shown that lobule-alveolar growth is induced in hypophysectomized rats injected with estrone and pure lactogenic hormone or with estrone, progesterone, and pure lactogen. These data do not support the concept that growth of the mammary gland is dependent upon pituitary hormones other than the lactogenic (302). The length of time elapsing between ovariectomy, or hypophysectomy, and the injection of substances causing mammary growth affects the response obtained (297, 301, 303). Testosterone propionate in young hypophysectomized male rats causes some development of the ducts and formation of secretory material (303), and in virgin female rats, when injected for twenty days, it

causes development of the acini of the mammary glands to such an extent that they lactate when exposed to suckling young (304). This growth is believed to be caused by the secretion of progesterone from the corpora lutea which hypertrophy during the administration of the androgen. Regression of the corpora lutea is accompanied by an increase in secretion of the mammary gland if androgen is given beyond twenty days. Reece has shown that the injection of diethylstilbestrol dipropionate either alone or with testosterone propionate causes growth of the udder and teat, and initiates and maintains lactation in multiparous dairy heifers (305). In virgin female goats progesterone and diethylstilbestrol, when administered for sixty days, stimulates the mammary gland to a stage comparable with that seen in mid-pregnancy. If diethylstilbestrol is given for an additional period of twelve days lactation, similar to that seen at parturition, is initiated (297).

It has been shown that the same daily amounts of purified lactogenic hormone and estrone which stimulate lobule-alveolar growth in hypophysectomized female rats are adequate for successful implantation of embryos (306). Studies on pregnant rats which were hypophysectomized and ovariectomized indicate that the placentae secrete substances which induce lactation and which also interact with estrone and progesterone to produce lobule-alveolar growth of the mammary gland (307). Administered lactogenic hormone causes an increase in milk produced by nursing and nonnursing mothers, and improvement in lactation in mothers who are not producing sufficient milk to maintain the life of their infants (308).

Although estrogens will cause growth of the mammary gland and milk secretion, they inhibit secretion if injected during lactation. Practical use of this knowledge has been made in preventing lactation following abortion (309), in puerperal women (309, 310, 311), and in the treatment of breast pain and engorgement (311).

Lactation which is impaired by adrenalectomy can be partly improved by those factors which relieve the symptoms of adrenal insufficiency (312). Adrenalectomy, however, of normal or castrated immature rats in which body growth is not markedly retarded, increases the number of lateral buds of the mammary ducts. This growth is increased further by estrogen (313).

Extension and confirmation of earlier findings concerning the noneffect of lactogenic hormone in hypophysectomized female guinea pigs has been reported and it has been found that adreno-

trophic hormone, adrenal cortical extracts, or 11-dehydro-corticosterone administered with lactogen induces lactation. Desoxycorticosterone acetate inhibits lactation in hypophysectomized and intact guinea pigs but does not induce lactation when given with lactogen (314).

It is well established that thyroid tissue, thyroxine, and thyroprotein have a stimulating effect upon lactation in dairy animals. However, the effect of the thyroid on the growth and development of the mammary gland is not so well understood. On the basis of results obtained in mice, it has been suggested that the enhancing effect of thyroxine on lobule-alveolar growth is that of superimposing the capacity of thyroxine to stimulate general growth upon the more specific lobule-alveolar effect of estrogen and progesterone, or of accelerating the rate of cellular reaction. The need of thyroxine for optimal growth of the mammary gland is shown by the relatively poor development of the glands in thyroidectomized mice given progesterone and estrone, or mammogen and estrone (297).

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EXERCISE

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War inevitably arouses a nation to an appreciation of its dependence for survival upon the physical vigor of its people. Notwithstanding mechanization of the military as well as the industrial base of modern war, a large section of the population is drawn into higher than customary levels of physical exertion. Particularly urgent, of course, are the problems concerning selection, training, and maintenance of fighting men. To solve these problems in human physiology and hygiene a mobilization of scientific personnel and resources has taken place, and a great many studies pertinent to this review have been carried out in civilian and military laboratories. Unfortunately, much of this work has not been published, because of general security regulations, but increasingly reports are now appearing in the journals.

This review deals with studies of man and intact animals in relation to fitness for, physiological and biochemical responses in, and consequences of physical activity.

Reviews.—The following reviews are pertinent to the present discussion: diet and physical performance, Henschel (1, 2), Johnson (3), and Keys (4); fuel of muscular exercise, Gemmill (5); fatigue and allied topics, Sayers (6); and Hellebrandt & Karpovich (7); exercise tolerance and medicine, Simonson & Enzer (8); and respiration in exercise, Comroe (9).

Physical Fitness Assessed by Exercise Tests

Strictly speaking, an exercise test measures only fitness for exercise, but since the daily life and work of man involves physical exertion to a greater or lesser degree, the relevance of these tests to general qualities of health and occupational fitness cannot be overlooked, if acceptable experimental and empirical evidence is offered. In these broader connections, reference is made to the discussion by Ivy (10) of applications to industry, to the test summaries and their interpretations for physical education by Cureton

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(11), and to the exhaustive paper by Simonson & Enzer (8) on exercise tests in medical science. These last authors emphasize the lowered exercise tolerance and easy fatigability associated with physical disease, because many physiological mechanisms of exercise are required as compensations to maintain adequate levels of resting function.

Maximal tests.—All tests carried to the point of exhaustion, whether the exercise is short and violent or long and grueling, are in this category. Seeking to minimize intraindividual variations in maximal work scores, Ivy and co-workers have employed a double work test with a ten-minute intervening rest period. Work performed before exhaustion in each of the two periods, the total work, and per cent recovery calculated from the formula: 100 (2nd work)/(1st work), yield four scores for analysis. In the original work (12) per cent recovery was found to be independent of training. However, the argument that per cent recovery is a more stable function of the individual than work output, based upon the coefficient of variation, cannot be accepted with confidence, because this statistic yields uncertain values when applied to variables having no "real" zero point. The significance of per cent recovery as an independent physiological measure of recovery is brought into question by: (*a*) the high negative correlation ($r = -0.95$) between per cent recovery and first period work output, confirmed, though not quantitatively, in later papers (13, 14); (*b*) the finding that pervitin, administered before the test, increases both work outputs but decreases per cent recovery (14); and (*c*) its lack of sensitivity to the following influences: pretest anoxia (13), amphetamine (14, 15), physical training (12, 15), and thiamine deficient diet (16). Work output data may be accepted on face validity, also the sum of two work periods probably increases reliability, and it is apparent that the authors have shifted their attention to this index of exercise tolerance. The slight negative correlations between total work output and an estimate of feeling tone ($r = -0.12$) and hours of sleep ($r = -0.25$) reported by Foltz, Jung & Cisler (17) are difficult to interpret, although the negative correlation with sleep may be related to insomnia-improved cardiovascular test scores reported by Henry (18).

Taylor (19) has used a maximal work test in which the rate of work on the treadmill is periodically increased until the subject becomes exhausted. The performance index, time-run to exhaus-

tion, is more reliable ($r_{11}=0.95$) than any of several physiological measures. Maximal heart rate, ventilation, blood lactate, and respiration rate did not correlate significantly with time-run, although small positive correlations were found with per cents oxygen and carbon dioxide, and oxygen consumption at the maximal point. These results in general agree with the summary of Johnson, Brouha & Darling (20), except for rate of pulse recovery, but Knehr, Dill & Neufeld (21) also have found rate of pulse return to be unrelated to maximal work output. Knoefel (22) has also used the increasing work principle in a bicycle ergometer test, but ten minutes after exhaustion again works the subject to exhaustion.

Johnson, Brouha and co-workers (20, 23) have presented a test based on a general pattern expressed by the ratio: (duration of effort) per (measure of physiological response). The exercise may be stool-stepping with or without load, pulling a "stoneboat," or a treadmill run, but the intensity in any case is so chosen that approximately one-third of the weakest subjects stop from exhaustion within five minutes. Others, strong enough to complete five minutes are stopped at that time, and test score is based upon physiological response, usually pulse counts early in recovery.

The original validation of the test scheme rests upon the treadmill work responses of men in selected fitness classes (23). Those in groups of lower fitness classification were exhausted in less than five minutes with maximal heart rates of 190 to 200 and blood lactates of 73 to 160 mg. per cent. Within these groups, however, heart rates and lactates are not significant variables, as shown in the data of Johnson & Brouha, especially when an error in calculating average lactate in group D is corrected (cf. 24), and as belatedly shown by abandonment of pulse counts on exhausted subjects (25). For those who complete five minutes of work, the score is inversely proportional to lactate and heart rate, as shown by average differences in the preselected fitness groups. Subsequently, the test has been adapted to field use (25, 26) and the following demonstrated relationships serve as empirical validations: effects of B-complex deficiency (20), comparison of male-female work output differences (27), relationship to strength of "masculine component" (28), and effects of physical training. In the latter case, the smaller training gains of high scoring men may more readily be accounted for by the limitations in the heart rate index of submaximal performance than the author's conclusion that the fitter sub-

jects had a lesser potential gain (26). The test has also been adapted for use on adolescent boys (25, 29), adolescent girls (30), and young women (31). Summarizing the evidence, it may be said that the Johnson & Brouha test has been shown valid only for broad group differences, and gives very peculiar distributions of scores in representative populations (26), due either to the dual criterion of scoring or to the illogical numerical combination of variables, such as time, heart rates, and lactates.

Kniazuk & Moliter (32) present a unique method of exercising rats in water under a load which lightens if they sink and increases as they rise in the water. "Endurance" and "peak load" variants of the test are described.

Athletic type physical fitness tests, when time and distance are made factors, may be considered maximal tests on the assumption that performance reflects physiological condition. The field is too broad for treatment here, but reference may be made to a concept of fitness based on such measurements by Larson (33); and to applications to college men (34, 35), the Air Forces (36), and the Ground Forces (37). Tunney (38) has championed the "setting up" exercise type and deep breathing.

Submaximal tests.—In the submaximal test a standard exercise is used and score is based on physiological response. Except for such applications as Master's post-exercise ECG test (39) and work tests of adrenal insufficiency (40), these tests are commonly supposed to assess general qualities of physical fitness. As such their validity must be established by correlation with reasonable criteria of fitness, and since in clinical and field applications only one test is generally given, it is necessary also to define the reliability of a single test score.

In a review of the literature on the Schneider cardiovascular test, Taylor & Brown (41) found the evidence for its validity satisfactory only when selected fitness groups were compared, but short of requirements for application to individuals. Tests on 325 young men demonstrate the Schneider index to be of low reliability and to be ineffective in predicting maximal exercise performance. That the index may fail to differentiate heart patients from normals, and to distinguish various types of circulatory disease, has been shown by Fiel, Petti & Park (42).

Kelly (43) has devised a fitness rating scale for girls based upon the recovery of heart rate and pulse pressure after a standard

exercise. Its designation as a test of "cardiovascular functional condition" on the basis of a favorable ten-case comparison between test scores and ratings by a cardiologist must be considered tentative until confirmed.

Using maximal treadmill performance as a criterion, Taylor (19) determined the validity of heart rate, oxygen consumption, ventilation, and blood lactate during and after submaximal treadmill walking. A negative correlation ($r = -0.56$) was found with heart rate, but a multiple correlation combining heart rate, blood lactate, and ventilation was not higher than 0.63. The intercorrelation between common respiratory, circulatory, and metabolic measures is such that a significantly higher multiple is hardly to be expected, thus accounting for the limited predictive efficiency of these submaximal measures.

Behnke (44) presents a stool-stepping test scored on exercise pulse change, rapidity of pulse recovery, and endurance time. Morehouse & Tuttle (45), in studies of post-exercise heart rate following various rates of stool-stepping, find that rates of 40 to 50 steps per minute are required for acceptable reliability. With lower intensities of exercise the pulse ratio is inversely related to resting heart rate, and this correlation is only reversed when exercise is made vigorous. This effect has also been noted by Phillips *et al.* (46). The effect of a simple uncomplicated common cold has been used by Henry (47) to evaluate several cardiovascular tests. Of these, only the pulse ratio test showed a significant response to the condition. More rapid respiration and shortened breath-holding times were noted. Changes in the same cardiovascular test scores after a sleepless night were also studied (18). Heart rates at rest and after exercise were clearly lower after loss of sleep. Consequently, improvement in scores was greatest in those tests in which heart rate is given most weight.

Differences in changes of blood constituents due to standard exercise have been related to fitness by several authors. Yanof (48) determined blood pyruvic acid before and at ten and sixty minutes after light exercise, using athletes, sedentary individuals, and cardiac patients. He found the post-exercise pyruvate content reduced in the wrestlers after exercise, and elevated similarly in the other two groups at ten minutes post-exercise. At sixty minutes, however, only nonhypertensive cardiac patients showed significant elevation. Crescitelli & Taylor (24) found significant

differences in average blood and urine lactate between selected fitness groups. The reliability of these measures compared favorably with that of other common physiological observations.

Other indices of fitness.—Resting pulse and blood pressures were not distinctly different in average college students as compared with varsity oarsmen in training (49). Pulse recovery has been shown to have limited validity after submaximal exercise (19) and after maximal exercise (21). Interest in oxygen pulse has been reawakened by Kibler & Brody (50) who show that the formula: O_2 pulse = .06 (body weight in kg.), holds for the range of mammals from the mouse to the elephant, and propose that the residual variation about this line be used as an index of muscular work capacity. In another investigation (19), however, this ratio was found to bear very low and only moderate correlations with maximal work performance when calculated respectively on submaximal and maximal exercise data. Respiratory efficiency, expressed as the ratio: (oxygen consumption) per (pulmonary ventilation), has been shown to relate to physical fitness by Barman *et al.* (51). Taylor (19) found only moderate correlations between this function and maximal exercise performance. Ryan & Ranseen (52) have studied the changes in palmar skin resistance (P.S.R.) during work on a bicycle ergometer, as affected by fatigue and amount of sleep. In alternate work and rest periods, P.S.R. rose with rest and fell with work. Changes in work output correlated intraindividually with changes in P.S.R., although the coefficients ranged from positive to negative and were in no case large.

Physiological Responses to Exercise and Associated Influences

Nutrition and metabolism.—Restricted protein has long been recommended for men working in the heat on the assumption that specific dynamic action of this food element appreciably adds to the heat load. Pitts, Consolazio & Johnson (53), however, found no essential change in fitness for work in hot-dry or hot-humid environments when dietary protein was varied from 76 to 105 and 149 gm. per day, although a 4 per cent higher work metabolism was associated with the highest protein intake.

Claims for a special work-increasing or fatigue-delaying effect of gelatin or pure aminoacetic acid have been refuted by a number of recent studies, including strength, maximal output, and endur-

ance tests (54 to 57). The theory of the alleged benefit is seriously questioned by Horvath (58) who found that neither total creatine nor phosphocreatine concentrations in rat gastrocnemii were affected by gelatin feeding. The subject has been critically reviewed by Keys (4).

An investigation which resulted in finding 26 per cent greater work output when 250 cc. of undiluted grape juice was given to subjects before work after an 8-hour fast, as compared with outputs of subjects receiving no substance, must be considered "justification research" (59).

Wrightington (60) found that the respiratory quotient of work and recovery tended toward a central value, 0.88 to 0.89, even though resting respiratory quotients ranged from 0.69 to 1.00 due to variations in diet. When the experiment was repeated after ingestion of 50 gm. of glucose, the work and recovery respiratory quotient rose to 0.92 to 0.93. No significant change in net mechanical efficiency was associated with sugar feeding. The finding that sucrose raised the resting respiratory quotient by 0.08 while glucose elevated it only 0.01 is interpreted by this author in terms of carbohydrate-to-fat conversion.

Further evidence that ketone bodies are utilized in muscle metabolism has been found by Drury, Wick & MacKay (61). Both men and rats rendered ketonemic by fasting showed a temporary fall in blood ketone concentration after exercise followed by a rise. Neufeld & Ross (62) obtained similar results in human subjects on a ketogenic diet, and in fasted guinea pigs. The post-exercise fall is attributed to ketone oxidation, and the later supernormal phase to unmasking of increased production of ketone bodies by the liver. Drury, Wick & MacKay believe that epinephrine secreted in the presence of low carbohydrate is the stimulus to increased ketone-body production in the liver.

The occurrence of muscular weakness and wasting in frank B-complex vitamin or thiamine deficiency has led to studies of possible deterioration in physical fitness due to subclinical shortages. Johnson *et al.* (63) found a clear diminution in physical test scores in ten subjects who entered upon a week's regimen of manual labor coincidentally with a B-complex restricted diet. Half the subjects who received a supplement of 2 mg. of thiamine hydrochloride daily showed slightly better performances. Addition of 18 gm. of yeast restored work outputs to pre-experimental levels.

Keys and co-workers (64) sharply criticized this study on technical grounds and have reinvestigated the problem of short-term deficiency with quite opposite results. Their subjects, put on a thiamine and riboflavin deficient diet, displayed no change in work capacity, psychomotor test scores, or clinical condition during the two weeks' deficiency period. They conclude that diets containing about one-third of the recommended optimum intake of vitamin B do not lead to deterioration in physical capacities within one or two weeks. Indeed, spontaneous activity and general excitability may increase in B-complex deficient rats (65).

On the other hand, B-vitamin deficiency over longer periods does produce deterioration in fitness for exercise. Barborka, Foltz & Ivy (16) found significant reduction in "double work" performances of subjects on a reduced thiamine, riboflavin, and ascorbic acid intake during a twelve-week period. Egana *et al.* (66) reported moderate reductions in physical fitness and easy fatigability in sedentary subjects on a B-complex deficient diet. The full effect of thiamine deficiency on work performance in rats is reached in three to four weeks (32). That fortification of normal diets with vitamins, however, does not improve fitness for work and exercise has been shown in static and dynamic work tests (67), muscular endurance tests (68), heavy industry (69), and treadmill running tests (70). Keys and co-workers (71) found no reduction in work capacity of men fed on one mg. riboflavin per day for periods up to 150 days. Significant reduction in performance of a physical task due to nicotinamide deficiency has been claimed by Frankau (72).

Wald, Brouha & Johnson (73) maintained human subjects for six months on less than 100 international units of vitamin A after a preliminary massive dose period of thirty days. No effect on scores in moderate and exhausting work tests was discerned. In studies of the ascorbic acid requirement for work in the heat, Henschel *et al.* (74) found that men receiving only 40 mg. of ascorbic acid daily did not differ significantly in fitness for exercise, nor in susceptibility to heat exhaustion, from men receiving 540 mg. daily. Rats on a diet deficient in vitamin E had a diminished capacity for treadmill running which could only be partially restored with *a*-tocopherol (75).

The energy cost of swimming, determined from oxygen debts

accumulated while swimming with the breath held, increases rapidly with speed in expert swimmers, but the cost may be five times as great in inexpert swimmers, according to Karpovich & Millman (76). At speeds of five feet per second metabolism may exceed 100 times basal.

Respiration and oxygen.—Comroe (9) has reviewed changing concepts of respiratory regulation during exercise. Following Harrison's discovery of augmented ventilation due to manipulation of a dog's limb with intact nerve supply but with interrupted circulation, Comroe & Schmidt (77) sought without success to find a peripheral chemosensitive reflex capable of evoking this effect in a variety of experiments on animals and men. Barman, Moreira & Consolazio (78, 79) reemphasized the central effect by repeating an old finding that occlusion of blood flow to working muscles depresses ventilation, but on restoration of circulation, the ventilation augments beyond the preocclusion level. That low oxygen tension, not anoxemia, is an effective stimulus to respiration has been shown by Asmussen & Chiodi (80). The response of ventilation to exercise is not different from normal when anoxemia is created by carbon monoxide poisoning, but is exaggerated when anoxemia is produced by lowered oxygen tension in the inspired air. In blood concentrations over 50 mg. per cent, lactic acid appears to stimulate respiration.

In the reduced oxygen atmosphere found at altitude, work capacity is greatly diminished, breath is short, and maximal lactates and heart rates reduced. Dill (81) points the parallel between these physiological responses and the effects of exercise on old men in a state of normal health. Hall & Wilson studied the ventilation and the maximal inspiratory (peak) flow at pressure altitudes up to 40,000 feet in working subjects breathing pure oxygen. Both ventilation and peak flow were unchanged to 30,000 feet but rose markedly at 40,000 feet (82). Previous exposure to anoxia at a pressure altitude of 18,000 feet for one hour reduced work capacity in three or four subjects in a double work test conducted within one half hour after return to sea level (13).

Temperature regulation.—Winslow & Gagge (83) have studied thermal interchanges between working man and his environment by the method of partitional calorimetry. Convection and radiation losses remained approximately unchanged as work metabolism

varied from 169 to 424 kilocal. per square meter per hour. Increased sweating balanced the heat production, and hyperthermia did not occur except at the upper range of work loads. Skin temperature did not depart notably from resting levels, but rectal temperature rose appreciably in work, indicating that internal, not skin temperature, was the effective stimulus for sweat secretion. Strenuous work in the heat, however, finds the big man at a disadvantage. Robinson (84) compared treadmill performances of two subjects differing by 38 kg. in body weight but of similar degrees of physical fitness. Heat production in both men was about equal, but the larger man, in whom the ratio of weight to surface area was 20 per cent greater, was forced to terminate a strenuous work test after seventy-five minutes with an excessive heart rate and markedly elevated skin and rectal temperatures. The smaller man, under the same conditions, achieved a steady state of temperature regulation and heart rate.

Attention has centered on the problem of physical fitness of men, whose accustomed habitat is the temperate climate, for the rigors of military campaigning in desert and tropical theaters of war. Racial and other innate characteristics may be important, but studies thus far have failed to disclose clear cut physical and biochemical factors (85), except for hereditary absence of sweat glands [Sunderman (86) has recently described several cases of this] and body size (84). Bean & Eichna (87) believe that the general level of physical fitness in part determines ability to work in the heat, but Taylor and co-workers (88) were unable to predict performance in the heat from the resting and work heart rates and rectal temperatures obtained in a temperate environment.

Acclimatization to work in the heat, on the other hand, is not only most striking from performance and physiological standpoints but is also of great practical importance. Most authorities are agreed that the major change in work capacity occurs within a week (87, 88, 89) and thereafter accrues more slowly. Acclimatization can be produced about as readily by part-time exposures to work in the heat (89) as it can be by continuous living and working in the heat (87), but continuous exposure to heat without working makes only a small contribution to acclimatization.

On first exposure to heat, work capacity is limited. Heart rates rise to excessive levels, hyperthermia occurs, and heat prostration

may ensue. According to Taylor, Henschel & Keys (88), these early effects are chiefly circulatory, occasioned by the greatly augmented cutaneous blood flow to eliminate heat and the failure of venous return. They find exaggerated Crampton reactions and greater incidence of postural syncope. A striking observation during the initial exposure period is marked flushing of the face and head, which moderates with acclimatization (87). Indeed, the average skin temperature may rise to 103° F. (89). Following these first adjustments, work heart rate and rectal temperature decline, and circulatory collapse is much less frequent.

A later adaptation is increased sweat loss and reduced salt concentration in the sweat (85, 88, 89). A more rapid onset of sweating promotes evaporative loss before body temperatures rise markedly (85).

The relative efficacies of water, salt, and glucose in the maintenance of fitness for work in the heat have been investigated by Pitts, Johnson & Consolazio (90). They found that supplements of salt or glucose have an insignificant effect in comparison to water intake. Taylor *et al.* have established that a moderate sodium chloride intake of about 15 gm. per day gives measurably better work performance than a low intake of 6 gm., but no advantage is gained by raising the intake to 30 gm. (91). Thirst is not an adequate guide to optimal water intake, since men may drink voluntarily only 50 per cent of what they lose in sweat (87). Forcing the intake to equal the loss, however, greatly improves performance in the heat (87, 90), while abrupt restriction of water imbibition induces the responses associated with the unacclimatized state (87).

Acclimatization developed by work in dry-heat is carried over to performance in humid-heat (87). The rate of loss of acclimatization to work in the heat has engaged attention (87, 89, 92). Decline in performance, though not great in one week, is marked in three to four weeks.

Circulation and blood.—Essex and co-workers (93, 94, 95) have measured coronary circulation of dogs trained for treadmill running by a modified Rein thermostromuhr applied to the circumflex branch of the left coronary artery. Earlier investigations which emphasized alterations in heart rate as determining variations in coronary flow were confirmed. Sympathectomized and unilaterally vagotomized hearts behaved like intact hearts, but total vagotomy

suppressed cardiac acceleration and with it increase in coronary flow, which appeared under these circumstances to be determined chiefly by blood pressure. Atropine sulfate also increased heart rate and coronary flow, this fact confirming vagal control of coronary flow, but the intermediate mechanism is yet obscure (93). However, Greene (96) suggests, on the basis of observations of coronary dilatation coincidental with voluntary muscular movements in lightly etherized dogs, that reflex increase in coronary flow is a primary accompaniment of muscular activity.

During the first week of a sojourn at 14,000 feet, cardiac output during work and rest rose to a peak then fell to an acclimatization plateau somewhat above the sea level value. Blood volume took an inverse trend, while oxygen capacity rose rapidly then reached a near plateau. The blood volume alterations are considered by Asmussen & Consolazio to regulate the oxygen capacity of the blood in the presence of cardiac output changes during early acclimatization (97).

Heart rate acceleration patterns during an exhausting treadmill test on thirty subjects have been correlated with endurance time, and a multiple R, of 0.90 developed between the endurance time criterion and a combination including submaximal heart rate, the second derivative of a cubic fit to the heart rate curve, and the heart rate at midpoint of the maximal exercise (19). Barrow & Ouer (98) in ECG examinations of 100 men after participation in athletic sports found (*a*) no change in atrioventricular or intraventricular conduction times, (*b*) voltage changes, but no inversion in the T wave, and (*c*) alterations in the size of the QRS. Master (39) noted T-wave obliterations and inversions after a standard stool-stepping exercise, and considers S-T changes after exercise to be indicative of coronary insufficiency.

The relationship between change in blood lactic acid, and the combined changes in blood cell protein, serum protein, and bicarbonate, in the transition from rest to work of various intensities has been quantified by Turrell & Robinson (99). Buffering of lactic acid up to concentrations of 4 m.eq. per liter is fully accomplished by base bound as bicarbonate, but with higher concentrations, base is drawn from the blood proteins. The maximum blood lactate value measured was 22 m.eq. per liter with a corresponding serum pH of 6.7. Crescitelli & Taylor report maximal lactates averaging

218 mg. per cent with a range from 117 to 328. The magnitude of these values is attributed at least in part to the relatively large amounts of work performed before exhaustion ensued. The finding of Bang, that in submaximal exercise blood lactate rises to a maximum early then declines regardless of whether or not work is continued, is confirmed in these data (24).

Shock analyzed the course of serum pH and bicarbonate changes following stair climbing and arm exercise. Serum pH and oxygen consumption recovered more rapidly than bicarbonate. The pattern of acid-base displacement was similar to that caused by ammonium chloride but about ten times more rapid (100). These recovery phenomena have been compared to the characteristics of a hypothetical three-chamber system, representing muscle, blood, and kidney cells. Curves calculated on this concept agreed well with experimental data (101). Farris (102) found significant shifts in the leucocyte counts in intercollegiate athletes. Pregame lymphocytosis, due to emotion, was the rule, but was less marked in veteran players. Postgame lymphocytosis is stated to correlate with fatigue, and total leucocyte increase was proportional to the intensity of the exercise.

Stoner & Wilson (103) found the serum cholinesterase level substantially unaltered by exercise in the occluded arm of normal individuals. However, Croft & Richter (104) employing more strenuous arm and bicycle exercises found a rise in serum cholinesterase with a proportional fall of the substance in the corpuscles. The cause of this esterase shift is obscure, but its magnitude is not considered great enough to affect significantly the blood content of acetylcholine. Within wide limits the concentrations of muscle potassium and serum potassium did not affect the work capacity of rats (105).

Pharmacodynamics.—The effects of sulfonamide drugs upon exercise have been studied by Roughton and co-workers. Administration of sufficient sulfanamilamide to bring blood concentration to 3 to 4 mg. per cent increased the ventilation 25 per cent in moderate work and decreased carbon dioxide production in maximal work by 29 per cent. These effects are attributed to the action of the drug in poisoning carbonic anhydrase (106). Similar amounts of sulfathiazole and sulfadiazine, however, were without effect upon work capacity and changes in blood chemistry and respira-

tion were negligible (107). According to Macht (108), depression of spontaneous activity in rats occurs with any of these sulfonamides.

Amphetamine (benzedrine) in doses of 10 to 40 mg. inhibited voluntary muscular fatigue and abolished the fatigue associated with a previous exhausting effort (109). Increased work outputs of men working to exhaustion on a bicycle ergometer are also reported by Knoefel (22), but Ivy *et al.* obtained no significant effect of the drug in the "double work" test, either on trained (15) or untrained subjects (14). The ergogenic effect of desoxyephedrine, however, has been more consistently demonstrated (14, 22). Present opinion holds that these drugs tend to increase work output primarily by dulling the sense of fatigue (110).

Work output in the second period of the "double work" test was increased by intravenous injection of 0.5 gm. caffeine (12). When like amounts were given one hour preceding the test, no effect was found in untrained subjects (15), but a significant increase occurred in work of trained subjects (14), Samuels, Henschel & Keys (111) were unable to discern an advantageous effect of administration of 50 mg. methyl testosterone per day on the work performance or grip strength of four normal young men. Kotalik, Maison & Pfeiffer (112) found no effect of ergotamine tartrate injections in subjects trained for finger ergograph work, but significant increases in output followed intramuscular injections of 4 to 10 mg. of neosynephrine hydrochloride.

A muscular work test for quantitative assay of adrenal cortical hormones is described by Ingle (40). A unit of activity is defined as the work equivalent of a 0.2 mg. dose of 17-hydroxy-11-dehydrocorticosterone given twice to adrenalectomized-nephrectomized rats. Estimations are made from a dosage-work response curve. Ingle, Li & Evans (113) found that thrice daily treatments with 0.5 mg. of adrenocorticotropic hormone to hypophysectomized rats nearly restored work capacity. Shipley *et al.* (114) have found a cortin-like material in normal urine which gives work performance and other positive tests for adrenal cortical hormone activity.

Excretion.—Losses of water-soluble vitamins in exercise sweat have been the subject of several investigations (115, 116, 117), which agree in showing thiamine and riboflavin excretions to be

extremely small, the values ranging from 0 to 7 gamma per 100 cc. of sweat for the former, and from 0 to 0.7 gamma for the latter. Pantothenic acid was lost in amounts ranging from 2 to 30 gamma (117), and nicotinic acid losses ranged up to 100 gamma (116, 117). The sum of ascorbic and dehydroascorbic acid excretions was approximately 0.2 mg. per cent (115, 117). Sargent, Robinson & Johnson (117) discuss the technical problems involved in obtaining accurate vitamin analyses from sweat and conclude: (*a*) that losses in sweat are exceedingly small in comparison to vitamin losses in the urine; and (*b*) that such losses are unimportant in vitamin nutrition.

Eggleton (118) compared the urine phosphate, ammonia, and pH of urine after exercise, using tea and water diuretics. Postexercise tea diuresis was always greater than water diuresis by about 50 per cent, as was also true for chloride loss. The immediate postexercise inhibition of diuresis is attributed to renal vasoconstriction, the more prolonged phase to the antidiurectic hormone.

Age, sex, and race.—Braun reported the application of exercise pulse rate tests to children (119), and Dane found that the pulse rates, blood pressure, and breath-holding time of the McCurdy-Larson test changed during the period of pubescence in the direction of greater fitness as rated by this test (120). Jokl & Cluver (121) state that while puberty retards development of physical fitness in boys, it halts the trend in girls. Hellebrandt & Dawson report alterations in the exercise tolerance of Dawson with age. Performance, recovery, and "resilience" changes in the age interval of 41 to 68 years are noted (122). Landen found that training increases concurrent oxygen intake during exercise in older persons with some types of cardiac impairment and considers this a beneficial effect (123).

Metheny *et al.* (27) compared responses of seventeen young women and thirty young men to submaximal and maximal exercise on the treadmill. In general, the sex differences were similar to those found between men of low and high fitness for exercise. There was considerable overlapping between the groups, and the performances of the eight best women compared closely with those of the ten poorest men. The author concludes that physical fitness is a continuous variable without qualitative differences between the sexes. Somewhat similar results were obtained by Simonson *et al.*

(124), and Dawson (125) notes acceptance of the principle in the formulation of physical performance standards for young women in the Soviet Union.

In Negro-White comparisons of treadmill performance, Robinson and co-workers (126) found no difference in heart rate and ventilation, but colored subjects performed submaximal work with a 7 per cent lower metabolism and accumulated greater blood lactate in maximal work. The former is attributed to greater skill and therefore efficiency, and the latter to greater motivation. The superior ability of the Negro sharecroppers to work in the heat is in part due to greater efficiency, a higher ratio of body surface to weight, more dilute sweat, and greater water intakes (127). A psychological explanation is advanced for the frequent supremacy of the Negro in athletic competition (128).

The Consequences of Exercise

Effects of physical training.—Jointly conceived studies of the physiological and performance aspects of physical training have been reported by Robinson & Harmon (55, 129) and by Knehr, Dill & Neufeld (21). The studies have in common the following: (*a*) college students, unselected for athletic ability were used; (*b*) the duration of the training period was six months; (*c*) training programs primarily stressed track and treadmill running rounded out with gymnasium and other physical activities; and (*d*) the test exercises consisted of two grades of submaximal work and a maximal run on the treadmill.

The increased physical performance with training is reflected by an average reduction of one minute in mile running time from the second to the sixth month of training (129), and by a 50 per cent increase in the grade which could be negotiated at the standard speed and duration of the maximal treadmill run (55). A summary of the physiological results of training indicates: (*a*) that, except for a small but consistent reduction in heart rate, changes in resting functions are either nonexistent or slight; (*b*) that, in submaximal work, mechanical efficiency is increased and blood physicochemical factors depart less from their resting values; and (*c*) that, coincident with substantial training increments in maximal work output, maximal blood lactate, oxygen consumption,

and oxygen debt undergo increase. It is notable that Robinson & Harmon failed to observe significant training change in alkaline reserve, although an increase has long been accepted from European work (129).

Gains in athletic-type fitness test scores after three months of training, reported by Hughes, amounted to 20 per cent. Running and muscular types of endurance showed greatest improvement, and skill, agility, speed, and strength performances the least (34). Kistler reported a similar study, though only a 1 per cent gain in a distance run was recorded (35). Subjects trained for two months on the bicycle ergometer were capable of about three times the work output of untrained subjects (12). Specific abdominal and thigh exercises were effective in reducing the incidence of fainting on the tiltboard (130).

Maison & Broeker (131) studied training in finger work in the presence of ischemia and with intact circulation. Gains in output of the ischemic arm were less than 30 per cent, but the onset of ischemic pain was delayed and its intensity ameliorated. The load which could be carried in a steady state by the circulated arm increased with training about 100 per cent, thus indicating the preeminence of circulatory changes in training. Maison & Kotalik (132) further showed that the absolute power of muscle rose only about 30 per cent with training, but was indefinitely maintained in the posttraining period, while endurance depreciated rapidly to 50 per cent.

Fatigue.—In experimental and theoretical approaches to the problem of fatigue, attention now centers on the physical, mental, and emotional variables within the individual which determine work performance, and on the effect of various external stresses which modify the performance (133, 134). The fusion frequency of flicker has been correlated with the fatigue of physical work by Simonson, Enzer & Benton (123). They found increases in frequency after short vigorous or static work, and decreases after 670 meter runs. Brozek & Keys (135) were unable to obtain significant changes in fusion frequency after hard treadmill work, and question the value of the test for general fatigue. Burge (136) found a rise in scalp potential (over the area of the motor cortex) at the height of physical exercise, followed by a drop with fatigue and a

change in polarity at exhaustion. This reversal apparently disappeared with training.

Other acute and chronic effects.—The essential psychoneurotic nature of "effort syndrome" is now generally conceded, the affliction yielding successfully to psychiatric treatment. The strain of heavy exercise may be a precipitating but not a primary cause (137, 138). Parsonnet & Bernstein (139) analyzing the concepts of acute and chronic heart strain admit the reality of the former, but find no evidence for the latter. "Athlete's heart" is believed to be nonexistent, though hypertrophy without dilatation may occur in the athlete. Jokl & Suzman (140) discuss the mechanisms involved in acute cardiac collapse during physical exertion, listing vascular rupture and coronary abnormalities as the most common factors. They believe that a history of undiscovered heart disease is usually if not always a basic factor, and cardiac collapse may develop in an athlete whose performance has not been previously below par. Measurements of heart size in 233 athletes by orthodiagrams indicate moderate hypertrophy as compared with Hodges-Eyster standards. Such hypertrophy is judged to be normal for athletes (141). From ECG examinations of thirty-five boys before and after participation in amateur boxing competition, Butterworth & Poindexter concluded that trauma to the chest wall produced no significant effect on the heart (142).

Numerous observations are cited of loss of endurance and general deterioration in performance of athletes after donating blood, and standard exercise tests on five young men showed that such blood losses led to reduction of performance in endurance-type tests, but not in anaerobic work tests (143). Allen (144) found post-exercise orthostatic syncope in 17 per cent of young men run to exhaustion on the treadmill, but there was no significant relationship between this occurrence and treadmill rating. Gilligan and coworkers (145, 146) investigated hemoglobinemia and hemoglobinuria after exercise, and found them to occur typically only after walking or running of long duration. The appearance of hemoglobin in the urine was associated with no known pathology and is considered by these authors to be a benign accompaniment of exercise.

In a study of the mortality among 2,919 men who had participated in the Indiana high school state final basketball tourna-

ments, Wakefield (147) found that the players had a death rate from all causes considerably lower than is listed in current life tables. In the player group, the percentage incidence of deaths from external violence and cardiovascular-renal disease was higher and that from pneumonia lower than was true for the general population.

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AERO MEDICAL LABORATORY
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PHYSIOLOGICAL PSYCHOLOGY

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The most recent textbook of general physiological psychology is that by Morgan (1). It is addressed to undergraduate and graduate students who are preparing for work in psychology, physiology, or medicine. The first one hundred pages deal with the history of physiological psychology, general functions of cells, internal environment of cells provided by the fluid tissues, physiology of nerve cells, and structure and specific functions of the nervous system. Then follow about forty pages on somatic and behavioral aspects of phylogenetic and ontogenetic development in vertebrates. Next are seven chapters on the special senses, two on reflexes, postures, and cerebral motor functions, one chapter on emotion, one on sleep and activity, three chapters on instinctive behavior and body needs, three on learning, one chapter on aphasia, and one on symbolic processes. Its bibliography of 830 titles embraces old and recent articles down to 1943. Instructors who wish an up-to-date introductory textbook will find this satisfactory in scope and extensity. Still more recent is a short but excellent chapter on physiological psychology by Golla (2), published in the *Journal of Mental Science*. This chapter contains citations of literature from continental journals which hitherto have received but little notice from American reviewers.

Development of Behavior

Detwiler (3) has studied the development of feeding behavior in *Amblystoma* larvae from which the forebrain, eyes, and nasal organs had been removed in early embryonal life. The anlagen of these structures were excised while larvae were in Harrison's stage 21. Those surviving beyond the feeding stage devoured daphnia and enchytraeid worms and snapped at other moving objects. All relevant motor activities, such as lurching, engulfing, chewing, and swallowing, were carried out in normal, integrated manner, but with less than normal vigor. However, general locomotor activity, as well as the more specialized foraging behavior, were considerably reduced in amount. Because of this the total intake of food was re-

duced and, consequently, rate of growth retarded. It is apparent from this experiment that lateral line organs constitute a partially adequate receptor mechanism for the detection of food in motion, and, furthermore, that their development can go on in larvae deprived of the forebrain. But only with forebrain intact can larvae deprived of sight and taste obtain sufficient food for normal growth.

According to Sawyer (4) the enzyme cholinesterase is a biochemical criterion of functional capacity of the neuromuscular apparatus in *Amblystoma* larvae. During the early flexure and coil stages only a small amount of this enzyme is present, and until the S-flexure stage is reached there is little or no increase. At the latter stage and during development in subsequent swimming stages the amount of cholinesterase increases rapidly. When inhibitors of cholinesterase are put into the surrounding media, the attainment of motor capacity is held in abeyance, and upon removal of the inhibitor solution, the rate of recovery of neuromotor capacity parallels increase in the amount of enzyme present. More recently, Sawyer (5) performed a similar experiment on fundulus, an organism displaying considerable spontaneous activity prior to its earliest neurogenic responses. He found that the capacity for true reflexogenic activity, as evidenced by responses to light tactile stimuli, was accompanied by an increase in the amount of cholinesterase in the tissues and that the flutter and swimming reactions were attended by an ever increasing enzyme level. Physostigmine, a cholinesterase inhibitor, does not affect spontaneous movements in young embryos but does interfere with the development of truly neurogenic behavior. Among neuroanatomists there has long been general agreement that no reliable structural criterion of onset of functional capacity in embryos is available. Along with others, Coghill has suggested the possibility that the transition from an inactive to an active state is effected by some as yet unknown physiological agent. Thus, the findings of Sawyer are actually a milestone marking progress of our understanding of the development of locomotor behavior.

Two details from a posthumous publication of an unfinished paper by Coghill are of interest. He (6) presents experimental data from *Amblystoma* supporting the view of Head & Riddoch (1917), who interpreted involuntary reflex action of the paralyzed parts of the human body, following sectioning of the spinal cord, in terms

of the primacy of nociceptive reactions. Coghill says that flexion is the earliest type of response made by vertebrate embryos and that flexion is essentially nociceptive in nature by virtue of its being an avoiding reaction. Extension, which is concerned with posture and locomotion, appears much later than flexion. In this same paper Coghill observes that "inhibition" plays a special role in the process of individuation of behavior because " . . . development of the local sign is effected through inhibition. For normal functioning inhibition must be maintained according to the pattern of its ontogenetic development."

With Watkins, an earlier collaborator, Coghill (7) offers a speculation on the behavioral forerunner of sleep in developing amphibian larvae. These investigators repeatedly found pronounced periodicity in sensitivity to light tactile stimuli during that phase of sensory development which immediately precedes the attainment of minimal thresholds in different regions of the skin. There is a significant degree of synchronization of high and low sensitivity in embryos of the same age, despite different rates of development in different regions. Furthermore, beyond the time when minimal thresholds have been established in different areas there are periodic backward and forward swings in sensitivity from levels well above to levels right at minimal thresholds. These fluctuations are noticeably, although not perfectly, synchronized in different areas of the skin. The periodicity cannot be ascribed to fatigue. Hence, since this highly generalized process appears to reflect an intrinsic process, endogenous in origin and primitive in nature, such as the organic states associated with rest and activity or with sleep and wakefulness, the authors suggest that it may actually be a forerunner of sleep, the latter in its more characteristic form appearing at a later stage of development.

In keeping with several previous studies of rats which have been subjected to severe inanition, James & McCay (8) found no impairment in rate of acquisition of conditioned responses in dogs whose growth was retarded experimentally. Taking a litter of five Saluki pups, they held the weight of two of them at maintenance from the age of 107 to 207 days and thereafter allowed them to grow at somewhat less than the rate normal for animals of that age. The food ration for the two experimental and three control dogs differed only in amount. They began their tests for rate and quality of learning when the animals were 186 days old. Learning

trials continued until they were 445 days of age (maturity). No significant quantitative or qualitative differences in conditioning either positive or negative motor responses were found. Minor differences in behavior pertain chiefly to energy output. The undernourished animals, although no less alert than the controls, were unable to do as much work per unit of time or to continue their activities as long.

McGraw (9) has summarized a long series of investigations on neuromuscular maturation of the human infant which were planned and executed under her own direction but instigated largely by the late Dr. Tilney of Columbia University. The six brief chapters of her monograph deal with the structural foundations of behavior, neonatal behavior, development of neuromuscular activities, early sensory development, individual development, and learning. In the last chapter she gives behavioral criteria that indicate the readiness of certain neuromuscular systems (e.g., those for micturition, defecation, and walking) for further development through the process of systematic training. In this connection it is urged that reliable behavioral signs of maturational readiness in many other spheres be discovered so as to avoid wasteful and sometimes harmful efforts at training the child before the prerequisite neuromotor development has been achieved.

Brain Lesions and Altered Behavior

Although battle injuries have quickened human interest in the mental effects of cortical lesions, as yet this interest has not altered the prewar trend of animal experiments involving brain lesions. Allen (10), working with sets of from three to five dogs, conditioned them to respond differentially to pairs of cutaneous, auditory, and visual stimuli. Some were trained both before and after bilateral prefrontal lobectomy, and others, only after this operation. With but one exception the dogs were capable of making correct differential responses postoperatively. The exceptional dog inverted responses for positive and negative stimuli in the cutaneous series. In general, Allen claims that prefrontal lobectomy produces no permanent impairment in accuracy of differentiating sensory stimuli and only slight retardation in rate of acquiring correct responses.

Rats quickly learn, under appropriate training conditions, to operate a switch that turns off a bright light in their inclosure.

Ableman & Morgan (11) used this aptitude to determine whether differences in light aversion might be caused by lesions in various parts of the cerebral cortex. They found that bilateral lesions in the occipital region increased the frequency of light extinction in eight rats, as also did frontal lesions in two others. It decreased in frequency in three rats with prefrontal lesions in which there was partial interruption of the thalamocortical projections, but in one rat with parietal lesions no reduction in frequency occurred. Obviously these results are quite equivocal. They afford but weak support for the authors' belief that a specific light-aversion response is controlled by the prefrontal cortical areas in the rat.

Morgan & Wood (12) took advantage of the rat's tendency to alternate between right and left turns on a simple T-maze in order to determine whether this spontaneous alternation tendency is mediated by the prefrontal area of the cerebral cortex. If so, they reasoned, it would favor the hypothesis that immediate memory in the rat also is mediated by prefrontal areas because alternation would certainly require good immediate memory. They gave twenty-four intact rats ten opportunities to display alternation on six successive days. The time between the ten alternation trials was no less than fifteen seconds. Eighteen of the rats gave a greater than chance frequency of alternations, and thus qualified for the bilateral cortical operations, some being operated in the prefrontal or frontal, some in the parietal, and some in the occipital areas. On postoperative tests most of those receiving prefrontal lesions gave lower than a chance frequency of alternations in postoperative trials, whereas most of those with lesions in the occipital regions had frequencies higher than chance and only slightly lower than those of the original trials. Since it may be presumed that ability in the rat to alternate depends on immediate memory the authors infer from the foregoing results that immediate memory is mediated by the prefrontal areas. In the opinion of the reviewer, the data do not warrant this inference, for one should not assume that normal or operated rats which do not alternate spontaneously under certain conditions in a simple maze situation cannot do so. There are other well known causes for low alternation scores which in this study have not been excluded.

A still further attempt to localize mental processes in the cortex was made by Epstein & Morgan (13). It involved the change in rate of locomotion from start to goal in rats trained on an en-

closed maze with eight right and eight left turns arranged in alternation. Eight rats with small prefrontal lesions and eight normal controls were used. In the experiment proper five trials per day were given in close succession, for a period of thirteen days. The time scores show that during days 1 to 5, both control and experimental animals displayed a positive goal-directed speed gradient on each of the daily trials. During days 6 to 9 the controls still displayed the positive goal gradient for the first three-fourths of the run but began to decelerate in the last quarter. Terminal deceleration (called anticipatory gradient) increased steadily in amount from the first to the fifth daily trial. During days 10 to 13 the terminal deceleration (called anticipatory gradient) appeared somewhat earlier than theretofore in the runs and became accentuated with advancing days. In contrast to the normal rats, the prefrontal cases displayed a speed gradient throughout trials 6 to 13 that was even more pronounced than that displayed during their first five trials. The authors say that

> The anticipatory gradient studied here may be taken roughly as the foresight and preparation for the eating of food in the goal box. The total destruction of this ability (foresight) in the operated rats has been clearly demonstrated in the results.

The legitimacy of this rather sweeping conclusion is questionable. A difference in performance has been clearly demonstrated, but the inference that terminal retardation by the normal rats denotes foresight requires substantial proof beyond mere naming of a tendency in behavior. Furthermore, to locate the ability in the prefrontal areas is highly conjectural, in the absence of systematic experiments involving lesions in the other well known areas of the cortex.

Continuity of Lashley's interest in the role of the cerebral cortex in maze performances of rats is indicated by two substantial papers. Using his relatively simple alley maze with alternating turns, Lashley (14) compared the amounts of impairment in maze learning performance resulting from (*a*) enucleation of both eyes, or peripheral blinding, (*b*) sectioning the posterior thalamic radiations, and (*c*) bilateral destruction of the area striata. Black rats from a mixed strain were used. Lashley concluded (*a*) that peripheral blinding hampered their maze proficiency about one tenth as much as destruction of the visual cortex plus the slight, unavoidable injury of adjacent structures, and (*b*) that sectioning of the posterior radiations, combined with slight unavoidable damage to

hippocampal lobes, auditory and postauditory cortex, and radiations from underlying nuclei, caused the same amount of deterioration as peripheral blinding. Further investigations, involving the area striata alone, and this in combination with adjacent areas, led to the conclusion that "the visual cortex has some important function in maze learning which is exercised in the absence of any visual stimuli." In a second study Lashley (15) separated many adjacent architectonic fields of both hemispheres by knife-thin incisions through the cortex and its underlying fibers. The object of this procedure was to determine the degree of participation of different cortical areas in maze performance. Thirty-two rats learned the same alley maze as that in the foregoing study. Then they were allowed a 14-day lay-off, followed by a series of retention trials. Next, in the following order, came the cortical operations, a 14-day recovery period, and finally the postoperative retention trials. A second group of twenty-five rats was similarly operated and, after fourteen days, subjected to initial learning trials. These two groups provide an adequate basis for the estimation of losses in initial learning as well as losses in retention of habits formed prior to their operations. Despite bilateral separation of adjacent architectonic fields normal records were made by certain animals. In all cases having some impairment in learning, the decrement was ascribable to interruption of thalamocortical fibers or to destruction of cortical tissue rather than to the interruption of transcortical connections *per se*. This finding corroborates a conclusion reported about one and a half decades earlier, but less satisfactorily established by Lashley.

Differences in "initiation" or starting of simple responses was found by Harlow & Johnson (16) in two monkeys from which the prefrontal lobes had been removed. They were compared with two normal animals as to promptness of reaching for food exposed for periods of ten, five, three, two, or one seconds in random order on the right or left side of a food box. On all but the one second exposure the operated and normal animals were similar in successes. At one second the operated animals made significantly more failures. Since the requirements of the problem were such as to obviate formation of new associations, discriminative acts, or symbolic processes, one may assume that failures were simply in respect of initiation of the act of reaching. The authors remark that failure in certain very simple aspects of a problem may predicate

failure in the more complex elements of tests regularly given animals in our laboratories today.

Using the same operated monkeys described above, Harlow & Spaeth (17) determined their ability to master a series of problems in which a stimulus was allowed to acquire multiple sign values. The series of tests was so designed as to provide an increase in complexity of factors designating the correct response. Quite probably these tests are among the most abstract and complicated ever successfully used with infrahuman subjects. On all of the tasks the two monkeys which had been deprived of prefrontal lobes displayed levels of abilities heretofore only rarely seen in normal infrahuman subjects; nevertheless, they were inferior to the four normal animals similarly tested. The authors describe the remarkable performance of both operated and normal animals to careful gradation of the difficulty of tests. Without gradation, incompetence and disabilities are likely to be exaggerated, they say.

Golla, Hutton & Walter (18) have reported constant physiological concomitants of mental imagery. They investigated the imagery of human subjects in seven different tasks, such as mental arithmetic, thinking over a fairy story, a plan, or an argument, and recalling a hymn and a poem. Of sixty-one males, twenty-five had regular respiratory rhythm, and of these only two used laryngeal kinesthetic images as judged from their responses on the seven tasks. Thirty-six males had irregular respiratory rhythm, and of these thirty-two used laryngeal kinesthetic images. Of thirty-seven females, twenty had regular respiration and none of these used laryngeal kinesthesia; seventeen had irregular respiration, and of these, eleven used laryngeal kinesthetic imagery. The alpha waves of sixty subjects suggest that there is a low degree of correlation between EEG and imagery type, for those with pure visual imagery tended to have extremely small alpha rhythms (below 10 microvolts), and those with pure auditory-kinesthetic imagery tended toward persistent alpha records, regardless of mental activity. The alpha records could be divided into three types: M, extremely small; R, responsive, with clearly visible rhythm when the subject's eyes were shut, but blocking or attenuation when eyes were opened or mental exertion called for; and P, persistent, regardless of mental activity or whether eyes are open or shut. There is a difference in the responses of men and women if one uses this basis of classification. The proportion of R and P responses is

lesser and of M responses greater in women. This study of a much investigated problem in psychology is thought-provoking. One of its chief weaknesses, however, is inherent in the method of testing imaginal types. The problem should be investigated further, using more definitive tests of imagery, such as those worked out in psychology laboratories about four decades ago.

Food Hoarding; Appetite; Effects of Inanition on Behavior

It has long been known that wild and semidomesticated laboratory rats display a tendency to hoard food. Until recently, however, but little has been done to determine the etiology of this type of behavior. Morgan, Stellar & Johnson (19) have made a promising beginning. They performed four experiments to establish the amount of correlation between (*a*) onset and rate of hoarding and (*b*) length of food deprivation and degree of hunger satiation. Albino rats were given daily tests for hoarding after a twenty-three hour period of food deprivation which had been followed by one hour for eating or for hoarding, the preferred activity resting solely with the animal. They found that the number of days before hoarding began in this experiment was highly variable from individual to individual. After appearing, however, it was displayed quite regularly, whether the tests followed a 12, 24, 36 or 48 hour deprivation period. The authors found that the initial awakening, as well as subsequent arousal of hoarding, depends chiefly upon the cumulative effects of deprivation rather than upon acute hunger. They also found that eating conflicts to some degree with hoarding. This was indicated by the fact that when rats were allowed a half-hour eating period before hoarding tests began, a higher per cent did some hoarding than when no prior period for eating was permitted; also, the number of pellets assembled was greater. Other incidental points reported in the study are as follows: rats store more pellets during morning than during night hours, possibly because they eat more during the night; removal of pellets by the experimenter while the animals are hoarding has no influence on the total number assembled in a given test; in females, hoarding is more readily initiated than in males; also, with females there are fewer failures to hoard in a series of tests, and the number of pellets gathered is greater than with males.

In further experiments Stellar & Morgan (20) attempt to de-

termine the relative importance of hoarding experience *per se*, and length of food deprivation upon frequency of the hoarding response. Three groups of rats were subjected to preliminary study during a period of eighteen days. Daily, during this period, group 1 was deprived of food for twenty-three hours, then allowed to eat for a half-hour, and finally tested for hoarding during the remaining half-hour. Group 2 which had food available at all times was given merely a daily half-hour hoarding test. Group 3 underwent a twenty-three hour period of food deprivation before the half-hour eating period, but was not subjected to tests for hoarding. At the close of the preliminary phase all groups were subjected to the same kind of hoarding tests. For eight successive days, each rat was deprived of food for twenty-three hours, then allowed a half-hour to eat, and finally, a half-hour in which to hoard or not to hoard, at will. Scrutiny of the results from the preliminary study reveals that almost all animals of groups 1 and 2 had displayed the hoarding response at some time; thus by definition they qualified as experienced hoarders. None of group 3 had had any opportunity for hoarding prior to the final eight-day series. Nevertheless, in group 3 a significantly higher per cent began to hoard on the first day of the main test than had been the case in either group 1 or 2 at the beginning of their preliminary tests. Furthermore, in group 3 the per cent was higher than in groups 1 and 2 on the first day of the comparable eight-day series. From these findings, the authors conclude that the cumulative effect of deprivation is the primary factor in arousing the hoarding response, and that exercise of this function is subject to satiation. The latter was evidenced by the observation that the experienced hoarders of groups 1 and 2 actually hoarded less in the eight-day series than the previously inexperienced animals of group 3. Continuing, they say that hoarding, once initiated, is a tendency which waxes in strength if opportunity to exercise it is denied and wanes in strength after opportunity for its exercise is allowed for a brief period of days.

To elucidate the physiological mechanism of hoarding Stellar (21) studied the effects of injections of epinephrine, insulin, and glucose. Because of the positive relation between duration of food deprivation and onset and level of hoarding, and the fact that fasting tends to deplete the glycogen reserve, the authors surmised that hoarding might in some way be related to concentration of carbohydrate in the tissues. If so, it might be expected that glu-

cose and epinephrine would decrease hoarding by raising the carbohydrate concentration in the blood and other tissues; and insulin, on the contrary, would increase hoarding by producing hypoglycemia. Using but one drug on each animal and alternating injections of this drug with saline so that each rat was its own control, the author found that a small but statistically significant decrease in hoarding was caused by epinephrine, but that hoarding was not significantly affected by insulin or glucose. Since this experiment had certain technical shortcomings, the author advises that further studies along the same line be made.

Dove (22) has devised a technique for study of food habits which combines psychological and nutritional measures in a single end-result called "apetitional levels" of food consumption. Using 228 natural foods, the author determined the lowest and highest rate of consumption for each. When the appetite levels of each of the 228 foods which would meet the calorie need of the subject to the extent of 100 per cent were determined, it was found that these same foods supplied the subjects with more than 100 per cent of human requirements of protein, of the vitamins A, B_1, C, and G, and of the minerals calcium, phosphorous, and iron. Thus when natural foods are compared in terms of their nutritional contributions at appetite levels of consumption, they may take on an entirely different order of value from that based on nutrients per unit of weight. Some classified as poor sources, according to nutrients per unit measure of weight, may, on the basis of appetite levels, be classified as excellent sources, and vice versa. Dove suggests that malnutrition considered as a bioeconomic problem would appear to secure some of its chief preventives and correctives through wider availability of foods possessing original nutrient values in patterns adjusted as closely as possible to appetite levels of normal healthy individuals.

Interesting but less scientific than the foregoing is Wallen's (23) study of sex differences in food aversions. Using a check-list of 143 foods, he gathered data on the aversions of 237 male and 308 female college students. Analysis led to the following conclusions: (*a*) a rather high degree of uniformity exists between masculine and feminine dislikes for foods, yet reliable differences are found for a very small proportion of items, and (*b*) in most instances of reliable sex differences the females exceed the males. Here, one may suggest parenthetically, a supplementary study such as that

by Dove would be appropriate to determine whether the excess of food dislikes by females actually produce a less wholesome diet than that of the males when comparisons are based on appetitional levels of consumption. Wallen, speculating as to the cause of these sex differences, says that they can be accounted for by assuming that social pressures tend to force males to discontinue total rejection of disliked foods, thereby affording opportunities for the correction of prejudices, whereas, in the case of females, social pressures permit the retention of habits of total rejection. No critical evidence favoring this assumption is given.

In times of accelerated industrial programs it is natural that interest in the relation of diet to fatigability and physical endurance has provoked several inquiries on the fatigue-alleviating possibilities of vitamin B_1. Valentiner (24) studied the effects of the B complex on fatigability of feebleminded children. Twenty pairs of mentally deficient children (median IQ of 65) were matched for age, sex, and socioeconomic status. All received a four ounce cup of tomato juice daily for eleven weeks. That consumed by the experimental group was fortified by a therapeutic dose of water-soluble liver-powder. Both before and after the eleven-weeks' period all of the children were given a battery of cancellation, color naming, and ergographic tests. The ergograph is the only genuine test of muscular fatigability. In this, no before-and-after difference between the two groups was found. On the other tests, however, interesting differences appeared. At the end of the eleven weeks the experimental group (fortified by liver powder) could maintain almost the same levels of speed and accuracy in the second half of their tests as were attained in the first half. Characteristically, the control group could not. Their second half performances at the end of eleven weeks were just like their own had been at the beginning of the experiment. The author believes that the liver powder (rich in vitamin-B complex) was responsible for sustained attention and prolonged mental effort in the feebleminded children. This potential benefit, if confirmed, may have considerable significance for the educational program of dullards in public and private schools. It would be particularly important to determine its potential influence on standardized test scores taken before and after treatment.

Using rats in a self-selection feeding experiment Warkentin, Warkentin & Ivy (25) compared choice and total food intake of

thyroidectomized and hyperthyroid rats with that of normal animals. No characteristic qualitative difference in food choices or in amounts of specific items eaten by rats with the two kinds of thyroid abnormality was found. However, as compared with normal rats, the thyroidectomized animals showed a marked decrease and the hyperthyroid rats a marked increase in total intake.

The appetites of adrenalectomized rats were studied by Clark & Clausen (26). Adrenalectomized rats were offered dextrose, salt mixture, yeast, casein, 3 per cent sodium chloride, water, corn oil, and codliver oil in self-selection containers. Their choices and total intake were compared with their preoperative intake and also with those of adrenalectomized animals that were receiving injections of suprarenal cortex hormone. The untreated adrenalectomized animals consumed more sodium chloride solution than they had eaten preoperatively, but those receiving hormone therapy did not differ from normal rats.

Work along the foregoing line has also been reported by Rice & Richter (27). Eight normal rats showed a sevenfold increase in appetite for a sodium chloride solution when given daily injections of from 2 to 4 mg. of desoxycorticosterone acetate. Four rats on a salt-poor diet that were treated with suprarenal cortical hormone showed no increase in fluid intake until sodium chloride was added to their drinking water. Four rats given a high salt diet and daily injections of 2.5 mg. of desoxycorticosterone acetate showed a 50 per cent increase in water intake. At the same time four control rats, on a salt-poor diet and tap water, showed no increase in thirst. These data, it is argued, show that the primary effect of desoxycorticosterone administration is an increased salt need which is accompanied by an increased appetite for salt. Polydipsia in such animals is a normal consequence of the increased intake of salt.

Work Fatigue: Efficiency

The most recent review of the entire field of mental work is that of Bills (28). This is a readable book written for the improvement of personal efficiency rather than as a technical resumé of experimental studies. The topics covered are: mental work and fatigue, rest and recovery, sleep, attention and distraction, motives, suggestion, age effects, and the nature of effective thinking.

Something new in point of view and methods of research on

fatigue as related to complex skills is found in the study by Bartlett (29). He remarks that skill-fatigue cannot be adequately understood or investigated by means of the old-time classical laboratory setup designed to measure increments in the performance of elementary movements or other activities. Since skilled operations in life settings involve complex, coordinated, and accurately timed activities that occur in response to stimuli which have the character of a field or pattern, experimental settings, to be adequate, must epitomize these life settings. This condition Bartlett and his associates established with a marked degree of success. He reports that, under conditions of skill-fatigue, the "standards" of performance accepted and followed by the subject unwittingly deteriorate. The limits denoting errors get wider and wider and, by virtue of this, a subject who is gradually failing may have an impression of doing better work. Prior to that time when amount of fatigue is very great, it is far more likely that right actions will be performed at the wrong time than that wrong actions will appear in the sequence. As advanced stages of fatigue appear, the stimulus field tends to lose its unitary character; it splits up, becoming a collection of unconnected signals for action, with some of these predominant over all the others, whether correct or not. Particularly, stimuli which are in the margin of the pattern, not closely organized with the central field, are ignored, with the unfortunate result that serious lapses of special actions occur. Sensations of bodily discomfort become more pressing and their claims on attention more insistent, thereby affecting the skilled performance adversely. Irritability is greatly increased. Verbal reports about details connected with known failure or error become less and less accurate. This study is especially relevant to skilled workers in wartime whose efficiency must be maintained at high levels, oftimes over long periods of time.

Foltz & Ivy (30) investigated the effect of simulated high altitudes on subsequent output of work. They used four experienced subjects on the bicycle ergometer and put them through a double work period. Exposure to an altitude of 10,000 feet for one hour without oxygen did not cause discomfort or affect their subequent work output. Exposure to 18,000 feet, however, caused cyanosis, headache, somnolence, nausea, visual disturbances, and palpitation, and a decreased work output on return to ground level in three of four men. A rest period of thirty minutes before beginning

work was insufficient for complete recuperation, and repeated exposures did not hasten the speed of recovery. The authors doubt that chemical changes in the muscle would be sufficiently persistent to account for the decreased output. The same may or may not be true of the cells of the central nervous system. However, after-effects of anoxia and hyperventilation could account for the decrease. If so, probably air-borne troops who have symptoms of anoxia or hyperventilation at any altitude would not be able to exert themselves normally for at least half an hour after experiencing the symptoms.

Graybiel, Horwitz & Gates (31) studied overfatigue in 172 student pilots. Overfatigue is defined as fatigue which is not relieved by a good night's sleep. Slightly over half of the student pilots admitted experiencing it. The most predominant symptoms are: subjective feelings of fatigue, increase in effort necessary to work, increase in irritability, tendency to fall asleep, tendency to become careless, loss of appetite, loss of weight, tendency to sigh more than usual, lack of desire for outside activities, increased consumption of tobacco and coffee, and an increase in the amount of alcohol used. Attempts to determine the predisposing factors to overfatigue by inquiries into the students' pasts and family histories yielded negative results. The precipitating factors appear to be as follows: long hours of duty, lack of sleep, difficulty in initial adjustment to advanced stages of training, anxiety associated with a hazardous occupation, long periods of idleness in ready rooms, and unsatisfactory relationships with instructors. Airsickness and the effects of acceleration appear to be unimportant in this connection.

Possibly bearing on the foregoing problem is the recent discussion of fatigue by Hoagland (32). He and his assistants found a high degree of correspondence between ability of men to withstand fatiguing ordeals and level of functioning of the suprarenal cortex. Hoagland says that "from 356 experiments on twenty-one healthy young men we have found, in most cases, marked improvement in target meter performance when they orally took fifty mg. per day of a pregnenolone." Their scores were not improved when placebo pills were taken. Also, in a group of over one hundred volunteer industrial workers engaged in a variety of operations and working under the incentive of piece work pay, there was a significant improvement in production rates and waste saving when they took pregnenolone as contrasted with placebos. The improvement seems

to be greatest when conditions of stress and fatigue are highest.

Evidence that diets deficient in the B complex affect performance under fatiguing conditions is given by Foltz, Barborka & Ivy (33). The performance of four trained subjects on the bicycle ergometer decreased significantly during a period of work while they were fed diets deficient in thiamine and riboflavin. No other objective signs of vitamin deficiency were detected, save slight increases in irritability.

To determine the psychological effects of the menstrual cycle on women workers, Seward (34) surveyed some seventy-two titles bearing on this topic. These studies were sifted for objective data on the effects of the menstrual cycle on production, absenteeism, extent of alleged "handicap," and the possible bearing of occupation on menstrual health. Seward could find in these studies only minor effects that are subjective in nature and merely restatements of the traditional view. Even objective studies of performance failed to reveal cyclic changes corresponding to the menstrual periods.

Mowrer & Jones (35) have related the rate of extinction of habits to the effortfulness of the task. They found that the rate at which a nonrewarded response extinguished itself was highly correlated with the effortfulness of the task. In explanation they suggest that elimination of a nonrewarded response involves a conflict in which the fatigue generated by the effortful task instigates a response (resting) which is incompatible with, and therefore tends to inhibit, the habitual response. They invoke the same hypothesis to explain the reappearance of an extinguished response after a lapse of time that is sufficient to allow the fatigue to disappear.

Kirkpatrick (36) reviewed twenty-two titles relating music to the health and output of workers in industry. The consensus of opinion is that music facilitates the socializing of workers and relieves boredom. Workers believe that music improves their feelings. It is most appreciated by those doing repetitive manual tasks and is most hindering to those whose work demands a high degree of mental concentration. It is suggested that music be presented on two or three occasions during the worker's day but for only comparatively short periods of time. Music time should be adjusted to output curves so as to offset decrements ascribable to ennui or fatigue.

Sex Drive and Reproductive Behavior

Cooper (37) has given a detailed description of parturition in a domestic cat. In an earlier report he described parturition in the lion. Although a chain-like succession of events was found, no highly stereotyped pattern of responses is characteristic of the cat.

From the Yale Laboratory of Primatology Nissen & Yerkes (38) present a summary on reproduction in chimpanzees based on data from forty-nine births. The mean gestational period is 228.7 days and the range, from 202 to 261 days. There is a tendency for early pregnancies to be longer than later ones, although exceptions to this rule are numerous. One or more births occurred during each month of the year. This together with other data clearly indicate that estrus and fertility are not restricted to month or season. Following parturition about half of the mothers ate a part or all of the placenta. It is believed that under more natural conditions the proportion would have been larger. The maternal interest and solicitude for offspring is variable from individual to individual but, on the whole, somewhat more strongly expressed by multiparous than by primiparous females. How much the conditions of husbandry affected maternal solicitude and care, as observed in this colony, is a matter for conjecture.

Beach (39) has added information on the effects of cerebral injury on sex behavior of rats. The author presents the hypothesis that "masculine mating behavior is mediated at least in part by the neocortex while the feminine copulatory pattern is relatively independent of this part of the brain." Eleven female rats were observed for detailed manifestations of masculine and feminine behavior both before and after cortical lesions involving from 37 per cent to 100 per cent of the neocortex. There was no postoperative loss of receptive feminine responses, although integration of the separate elements of the complex act was often defective and out of proper sequence. However, the loss of large amounts of the neocortex resulted in decrease in masculine sex responses, and 100 per cent removal eliminated it *in toto*. Presence of the neocortex appears necessary for effective courtship and sexual domination of a receptive female, although it is possible that the overt copulatory response might be executed without it. To insure that minor changes in the female's behavior were not due to deprivation of sexual hormone, Beach (40) conducted further studies on the female rat. Twenty virgin females, reared in segregation, were ovari-

ectomized when from three to four months of age. Thereafter, at fortnightly intervals estrus was induced by injections of estradiol benzoate and progesterone and, on each occasion, standardized tests were made to obtain preoperative data on the characteristic details and frequency of copulatory acts of each female. Then a part or all of the neocortex was removed. After allowing a short period of time for their recovery, Beach again induced estrus and repeated the tests. Analyses of data from seven females in which from 97 per cent to 100 per cent of the neocortex had been removed clearly showed that at times normal patterns of mating behavior can occur despite absence of the entire neocortex. There was no essential difference in the frequency of pre- and postoperative ear vibration, hopping, and lordosis (these being the most characteristic elementary acts in female copulation). However, there were some instances in which lordosis persisted over-long and ear vibration was increased in amount. Also, resistance by back-kicking was absent in some females and markedly reduced in the others. Again the author contrasts the female and the male, emphasizing the point that males do not execute the copulatory act after total loss of the neocortex.

Koster (41) also studied sexual behavior of normal, castrated, and sex-hormone treated female rats. The author reports that in the female both masculine and feminine erotism can be made to function concurrently, a point established by Kun about one and a half decades ago.

Myerson & Neustadt (42) discuss the biological and medical aspects of human bisexuality and homosexuality in the light of their data on 102 males showing homosexual conduct. Typically, the active homosexual has a high or normal androgen level and an excessive estrogen output. The passive homosexual, however, generally has a low androgen level and only a relative elevation of estrogens. The authors believe that the amount of androgens largely determines the vigor of the sex drive and that the absolute or proportionate amount of estrogens determines its direction. Accordingly, homosexuality may best be regarded not as a biological entity but as a quantitative deviation. Usually, the aberrations in proportions of androgen and estrogen hormones come too late in ontogeny to affect the anatomy of the subject. Furthermore, they state that homosexuality is not in itself a disease, although it fosters a psychopathic trend in the personality. No lasting cures of

homosexual adults were effected by hormone treatment, even though the proportions of sexual hormones in the body, as indicated by those excreted in the urine, could be made to conform to proportionate levels of normal adult males.

A very extensive study of behavioral sex development in adolescents, by the direct interview method, is that of Ramsey (43). This study deals with the physical and behavioral sexual development of 291 boys of the age range, ten to twenty years. The adolescents were drawn from middle and upper middle socioeconomic levels of a midwestern city. Ramsey determined proportions of each age group in which voice change, pubic hair, ejaculation, and nocturnal emissions first appeared. Also, the boys were asked to rate on a four-point scale their erotic responsiveness to a list of fifteen items (sex conversations, obscene pictures, nude art, literature, burlesque, dancing, etc.). The range of scores was greater for the adolescent than for the preadolescent population. On the behavioral side masturbation was reported as the most frequent sexual outlet (98 per cent reporting its occurrence by the age of fifteen years). Of boys eighteen or more years of age, 44 per cent admitted having had sexual intercourses. Unfortunately, this type of study, although probably much superior to those based on conventional questionnaires, may still be plagued by errors of testimony arising from inaccuracies of self-observation and infidelity of recall even though cooperation of subjects is above reproach.

The sexual desire of women during the menstrual cycle has been investigated by Daniels (44). He finds that fluctuations of the amount of sex hormone eliminated in the urine correlate with erotic phantasies and other psychological productions throughout the sexual cycle.

Haggan (45) inquired as to the sexual phantasies and desires of forty married women ranging in age from seventeen to forty-nine years admitted to a tuberculosis sanatorium. Twenty-five of them reported sexual desire at some time during hospitalization. Frequency of this experience, as reported, was about the same in all age groups up to forty but was most frequent in patients who had been married from only three to five years. Libido was reported as increased in three instances, decreased in eleven, and unchanged in thirty-six. Affective transfer from spouse was not frequent and when reported was directed to a member of the opposite sex. The

ectomized when from three to four months of age. Thereafter, at fortnightly intervals estrus was induced by injections of estradiol benzoate and progesterone and, on each occasion, standardized tests were made to obtain preoperative data on the characteristic details and frequency of copulatory acts of each female. Then a part or all of the neocortex was removed. After allowing a short period of time for their recovery, Beach again induced estrus and repeated the tests. Analyses of data from seven females in which from 97 per cent to 100 per cent of the neocortex had been removed clearly showed that at times normal patterns of mating behavior can occur despite absence of the entire neocortex. There was no essential difference in the frequency of pre- and postoperative ear vibration, hopping, and lordosis (these being the most characteristic elementary acts in female copulation). However, there were some instances in which lordosis persisted over-long and ear vibration was increased in amount. Also, resistance by back-kicking was absent in some females and markedly reduced in the others. Again the author contrasts the female and the male, emphasizing the point that males do not execute the copulatory act after total loss of the neocortex.

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author concludes that control or direction of sexual desire is less important as a factor in adjustment to sanatorium life than has usually been claimed.

The potent role played by androgens in arousing and sustaining sex desire in women is indicated by the study of Salmon & Geist (46). They considered the effects of androgens upon libido in one hundred and one women under treatment for various endocrine disorders. The androgens were administered intramuscularly, subcutaneously, and orally. All but thirteen of the one hundred and one women thus treated reported some increase of libido; twenty noted excessive lust, which subsided within from two to four weeks after discontinuance of the treatment. It is concluded that

> Androgens have a three-fold action, causing (a) an increased susceptibility to psycho-sexual stimulation; (b) an increased sensitivity of the external genitalia; and (c) a greater intensity of sexual gratification. Endogenous androgens in the normal mature woman may act as the physiological sensitizer of both the psychic and somatic components of the sexual mechanism.

Bearing on the subject of sexual motivation is the work of Greenblatt, Motara & Torpin (47). They found that injections of progesterone depressed excessive libido, while androgenic substances increased both sexual desire and feelings of general well-being. The women treated were within the age range of from twenty-five to fifty-three years. The authors obtained their most striking results by implantation of pellets of testosterone propionate. Erotomania never occurred, but almost every woman who, at some time previously, had experienced voluptuous sensations, but in whom these no longer occurred on sexual stimulation, reported a strong resurgence of sexual desire. In frigid women who had not experienced sexual desire the latter was not corrected by hormone treatment. In conclusion, the authors suggest that the function of an androgenous component in feminine libido has never received the amount of systematic study this subject deserves. Furthermore, they say, the psychotic tendency of nymphomania, certain types of frigidity, premenstrual tension, and incompatibility in married couples may prove to be more amenable to change by proper hormonal substances than by other means hitherto used.

An interesting psychosomatic correlation of emotional shock and endometrial change has been reported by Loeser (48). Four women whose menstrual periods always occurred quite regularly missed one period after an emotional shock. Histological examina-

tions of biopsy specimens revealed an endometrium at the stage it would normally have been at the time of the shock. The author believes that the emotional shock caused an immediate arrest of normal uterine changes by interfering with the functioning of essential hormones.

Influencing Behavior by Drugs

Using female rats, Dispensa & Hornbeck (49) attempted to influence the learning ability of offspring by douching the prospective mothers with acid or base solutions just a few minutes before the time of breeding. Offspring of the treated mothers were compared with normal controls as to learning performances on a 12-unit, multiple T maze. As measured by numbers of errors made from days three to twenty-one in the trial series, it was found that a 2 per cent lactic acid solution produced offspring with inferior learning rate (C. R. of 2.36), and those from parents treated with a 6 per cent base solution gave a better performance than the controls (C. R. of 2.12). Offspring of untreated mothers and males previously treated with sulfanilamide did not differ from their controls. Offspring of sexually precocious mothers (age of sires unreported) gave litters slightly inferior in maze learning ability, as indicated by a correlation of $-.39 \pm .16$. All of these differences are small and of a low order of statistical significance. Hence, in the opinion of the reviewer, these suggestions of deleterious influences must be regarded as highly doubtful until confirmed by repetition of the experiments.

Delayed effects of lead poisoning on mental development in children was found by Byers & Lord (50). The authors present a follow-up study of twenty children who had been hospitalized in infancy or early childhood because of lead poisoning. All were adjudged to have made a complete recovery from the poisoning when discharged from the hospital. Results from psychological tests and developmental observations are presented. Only one child was found to be progressing satisfactorily in school at the time of the follow-up study. On the basis of the clinical findings it is suggested that lead compounds in the circulation of an infant interferes in some way with the developmental changes normally occurring in the cortex and in a high percentage of cases prevents normal growth and development of the cortex.

A carefully controlled experiment on the effect of prolonged and

massive doses of phenobarbital to rats led Jones & Jones (51) to conclude that it produces no measurable effect on their learning of a simple visual discrimination problem. In this study adequate tests of learning, retention, and relearning were employed.

Trying to obtain objective data on the effects of certain analeptic drugs on revolving drum activity of rats, Tainter (52) made the following observations. The greatest increase over control records was noted for injections of cocaine. Caffeine, metrazol, and picrotoxin were ineffective. Amphetamine, ephedrine, and propadrine caused markedly increased running if injected in single doses, but tolerance and depressant effects were prominent with continued dosage. The author comments on possible differences in reports of drug action which may arise from the method of testing rather than be inherent properties of the drugs. He implies that each study should contain detailed information as to the methods and conditions of testing so as to make more intelligible the related studies from different laboratories.

Harrell (53) claims to have demonstrated beneficial effects of thiamine on the performances of adolescent children of an orphanage. Thirty-seven pairs of subjects were matched as to age, sex, size, intelligence scores, and ratio of present weight to "expected" weight. Attention was paid to diet, environmental influences, and motivation in order to prevent differential effects of these factors on the performance of the subjects on eighteen chosen tasks. Pills containing a daily dose of 2 mg. of thiamine were administered to the experimental group and similar pills without the thiamine were given to the controls. The subjects did not know to which group they belonged. The results show that in all of the eighteen tasks, involving a wide range of psychomotor abilities, the vitamin-fed group surpassed the controls. The degree of superiority ranged from 7 to 87 per cent. This is a remarkable gain. A confirmatory study is desirable for if the facts are essentially as reported here, they deserve widespread dissemination to those responsible for the diets of school children.

An earlier experiment by Flory & Gilbert had failed to indicate a significant differential in the group means of college students treated with amphetamine sulphate and then subjected to tests of reading, multiplying, and an analogies test. The subjective reports from experimental and control groups revealed quite variable ef-

fects from expectation and suggestion. In a more recent study, Flory & Gilbert (54) attempted to throw still further light on the earlier study. They divided a group of 129 students into three groups that were equated for sex and tested intelligence. All were tested during a two-hour period on three ten-second trials in tapping, a reading test, a vocabulary test, and an analogies test. At the beginning of the two hour session, one group was given 15 mg. of amphetamine sulphate, the second group, 5 grains of caffeine citrate, and the third group a sugar capsule. None of the subjects knew what their pills contained, and all were given to understand that the pill would be stimulating. The results indicated that the non-drugged group (sugar pill) improved as much in the tests as did the two drugged groups; the latter did not differ in any essential way, whether they received amphetamine sulphate or caffeine citrate. Although there were many interesting individual variations from group to group, the reported claims for clearness of thinking and rapidity of work were not substantiated by the group results.

Experimental Neuroses

Maier (55) in his first monograph on experimental neurosis in the rat called attention to abnormal fixations on maladaptive responses as well as to convulsive seizures. Curiously, for the most part subsequent experimentation has chiefly involved the topic of seizures. Possibly this arises from the popular appeal of spectacular phenomena.

In one of their first studies on animal neuroses Maier & Glaser (56) produced some evidence favoring the hypothesis that the tendency to display convulsive seizures under appropriate conditions of stimulation is inherited in rats, possibly as a dominant Mendelian character. More recent studies by Maier (57) and by Finger (58), however, indicate that the tendency does not behave as a simple Mendelian dominant and also that different laboratory strains differ markedly as to susceptibility to seizures from auditory stimulation. Furthermore, Maier is convinced that susceptibility cannot be explained in terms of "sensation-level" of audition, the latter being a viewpoint ascribed to Morgan & Galambos (59). Since susceptibility to seizures diminishes greatly in positive cases which are tested repeatedly between the ages of four and ten months, Finger (58) recommends that the age factor always be

taken into account in systematic accounts of audiogenic seizures. This point is especially relevant in studies of the role of heredity in susceptibility.

Additional facts on striking differences in susceptibility in different strains of rats have been brought forward by Griffiths (60). Of 141 trapped wild Norway and fifteen Alexandrine rats subjected to air blasts, key jingling, and the Galton whistle, not one displayed either the excited running, retreating behavior, or convulsive seizures. This is particularly puzzling in view of the fact that some of the most neurotic strains extensively studied in several laboratories were derived from crosses between wild Norway and Wistar albinos. Griffiths believes that susceptibility to seizures in the domesticated colonies derives from a combination of factors such as inbreeding of sensitivity to high frequencies, dietary deficiencies, confinement in small cages, lack of practice in meeting new situations, and endocrine changes. However, it is the reviewer's opinion that few, if any, of these suggestions have explanatory value for many of the results published by Maier and his colleagues or those of others working with albino and mixed strains. The fact that Griffiths' wild rats displayed a fighting tendency toward the sound-producing instrument should be given further consideration, for this alternative response may have served gradually to allay physiological tension, thereby removing a necessary forerunner of the convulsive seizure. As early as 1939 Maier (55) suggested that rats which fought the shock-grid did not develop convulsions in his conflict situation.

Unless forcefully reminded from time to time, we tend to ignore the marked degree of unpredictability with which seizures appear in rats from hour to hour and day to day even under the best standardized conditions. This kind of variability is strikingly illustrated by Mirsky, Elgart & Aring (61). Working with a large number of rats and mice they repeated tests for audiogenic seizures over a period of two hundred days, and finding great temporal variability and undividual unpredictability, they stress the importance of the experimenter's taking full account of this in all studies wherein attempts are made to evaluate experimental variables relating to incidence, duration, and severity of seizures. Fortunately, some of our better investigators are keenly aware of the significance of individual variability in experiments of this kind and have taken the precaution to provide ample control data and

to use appropriate statistical methods in analyzing their results.

Passing now to another topic, we may inquire as to what influence the convulsive seizures have on rats' behavior in learning situations or those requiring the use of knowledge previously gained. Maier & Wapner (62) have studied the possibility that maze learning might affect the rat's susceptibility to convulsive seizures, and, conversely, the possibility that quality of maze performance might be lowered by seizures. They found that more of the rats stimulated auditorily while running the maze had seizures than was the case when they were stimulated by the same instrument while at rest. The authors ascribe this result to the greater intensity of auditory stimuli applied when the rats were running the maze. The more intense stimuli were occasioned by the experimenters' desire to compensate for the large space occupied by the maze. Another finding was that rats which had experienced a seizure while running the maze showed greater deterioration in subsequent maze performance than did those which had not experienced a seizure under similar conditions. This was believed to be the result of fear attached to the maze situation rather than to genuine loss of knowledge of the maze pathway. Supporting this conjecture is the finding of Sisk (63) to the effect that exposure to audiogenic seizure producing situations away from the maze does not significantly influence the rate of maze learning. Sisk did find, however, a slight positive relationship between slow maze learning and susceptibility to audiogenic seizures. This possible relationship should be investigated more thoroughly with other mazes and different strains of rats.

While considering the possible effects of convulsive seizures on cognitive functions it will be of interest to note at this place two studies dealing with convulsions produced by other means. For example, Stainbrook (64) studied the effects of electroshock convulsions on maze retention in rats. Twenty-eight animals were required to learn a simple T-maze with two choice points under conditions of hunger motivation. Then the group was subdivided into control and experimental groups. The individuals of the latter group were given one electroshock convulsion daily for thirty days. Both groups were retested on the maze twenty days after the last convulsion of the experimental group. In the retention tests the time and error scores of the controls were significantly better than those of the electroshock group. And the error scores of the experi-

mental group were no better than those of the original learning period. Their time scores, however, were better. The authors cautiously avoid ascribing the decrement of the experimental group to after effects of electroshock *per se*, saying that it may have been due to "emotional" behavior induced by shock treatment. No critical evidence of emotional conditioning is supplied, however, to support this conjecture.

Working with dogs, Rosen & Gantt (65) investigated the effects of metrazol convulsions on conditioned reflexes in dogs. A course of twelve metrazol convulsions gave varying results depending on the type of dog. In general there was impairment of functioning in the direction of (*a*) decrease of excitatory conditioned reflexes; (*b*) loss of inhibition, resulting in lack of differentiation between positive and negative stimuli; (*c*) lengthening of the latent period; (*d*) predominance of the activity of some lower centers at the expense of the higher ones; and (*e*) a long period of recovery. Impairment of function lasted from one to six months, even in the most stable dogs. In an extremely excitatory dog, in which inhibition was poor, the lessening of the excitatory conditioned reflexes resulted in apparent improvement in the behavior rather than in impairment.

Queries as to the essential provocative conditions for neurotic behavior in animals continue to stimulate new kinds of experimental studies. Maier & Wapner (66) have inquired as to whether the rat can voluntarily take steps to prevent its having an audiogenic seizure. The rats were trained to run from an electrified grid to a shelter. After this habit had been established, they were exposed to auditory stimulation at the same time the grid was charged. Animals which used the shelter to protect them from shock had seizures, nevertheless, which inevitably forced them back on the grid. They had them about as frequently as under normal conditions. In these experiments it was apparent that seizures took control of the rats, regardless of the threat of punishment.

By drug treatment Cohen & Karn (67) attempted to reduce the susceptibility of rats to audiogenic seizures. They matched twenty-two pairs of albino rats that were highly susceptible to sound-induced seizures on the basis of age, sex, weight, and sensitivity. Then they injected the experimental animals intraperitoneally with 175 mg. of dilantin sodium per kilogram of body weight every other day for sixteen days and five hours after the

injections tested them for audiogenic seizures. The controls were similarly tested, but received no injections of any kind. The control groups exhibited eighty-one seizures in eighty-eight tests, but the experimental animals suffered but four seizures out of eighty-eight exposures to sound stimuli. Twenty-four hours after withdrawal of the drug another round of tests showed that the protection afforded by the dilantin sodium was only temporary. In forty-four tests given to both groups of animals, seizures were exhibited in 88.6 per cent of the opportunities. Roughly similar results were obtained by Shohl (68). She reports that ten rats known to be susceptible to audiogenic seizures showed an appreciable decrease in the incidence of attacks when daily doses of crystalline dilantin ranging from 64 mg. to 79 mg. per 100 grams of weight were administered orally in a dry food mixture. Doses of 25 mg. per 100 grams of weight had little if any protective action. She remarks that the effects may be similar to the protective action of this drug with human epileptic patients, wherein it acts, in part at least, as a depressant.

Working with cats Wikler & Masserman (69) determined the effects of morphine injections on the execution of learned responses and on the tendency to display symptoms of neuroses. In four out of five cats, morphine in doses of 1 mg. per kilogram of body weight regularly produced refractoriness to stimuli and diminution of activity. Learned responses were greatly impaired. The most recently learned and more complex habits disappeared first, and reappeared last, as the effects of the drug wore off. The disintegration of learned responses was usually complete within ten minutes after injection, while reversal of this process began three or four hours afterward. Experimental neuroses, produced by creating an impasse between conflicting motivations of hunger and fear, abated with injections of morphine and were replaced by adaptive patterns of behavior five or six hours after administration of the drug. In three cats the neurotic behavior appeared in full force after the effects of morphine had worn off further, although a cat which had been only mildly neurotic showed notable diminution in its abnormal reactions the next day.

Whether the cortex is essential for the auditory seizures was asked by Beach & Weaver (70). Three rats of unspecified breed in which there was great susceptibility to audiogenic seizures were subjected first to unilateral cortical ablation and then later to bi-

lateral ablation. Postoperative seizures were compared with those of the preoperative period and also with those of controls. From twenty-one to twenty-seven days elapsed between the last preoperative and first postoperative tests. Following the interval, seizures were more frequent in both hemidecorticated and control animals, but increase in frequency and promptness of seizures was greater in the operated rats. After another interval of eleven days tests were renewed, but without further increase in frequency or promptness of seizures. Removal of the remaining half of the neopallium was followed by still further increases in frequency, promptness, severity, and duration of the comatose condition following the attacks. It is apparent that the audiogenic seizures are not contingent upon the presence of the intact neocortex. Further generalizations should await more complete histological studies of the brains.

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DEPARTMENT OF PSYCHOLOGY
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APPLIED PHYSIOLOGY

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This review will be limited to certain phases of physiology of particular importance in wartime: aviation medicine, fitness and performance (industrial and military), and resuscitation. The effects of heat, cold, and exercise have been considered in other chapters of this volume; an excellent symposium upon the physiological aspects of convalescence and rehabilitation has been published elsewhere (1).

AVIATION MEDICINE

Of the basic problems of aviation medicine those relating to anoxia, oxygen toxicity, decompression, air sickness, and aerial transport will be considered. The literature on acceleration has been reviewed recently by Ham (2) and the effects of hyperventilation and cold are discussed in other chapters of this volume. Books dealing with aviation medicine have been published by Bauer (3) and Jokl (4). For a review of the German literature up to 1942, the reader is referred to the monographs of von Tavel (5) and Ruff & Strughold (6). Langley (7) and Robinson (8) have written historical reviews.

Anoxia

Resistance to anoxia.—Of interest has been the accumulation of evidence to indicate that the central nervous system may not be so susceptible to oxygen lack as had formerly been thought. Oster *et al.* (9) exposed cats to 2.3 to 5 per cent oxygen until respiration just ceased. They were able to return sixty-four of seventy animals to normal in 294 of 300 anoxic tests. Horvath and co-workers (10) observed seven men breathing 4.2 to 6.0 per cent oxygen on twenty different occasions. All of the subjects became unconscious, with anoxic exposures ranging from three to twenty-one minutes. No permanent harmful effects were detected in these individuals. Ward & Olson (11) reported the case of an aviator flying for thirty-nine minutes at 20,000 to 25,000 feet and for another sixteen

minutes at 12,000 to 20,000 feet, all of this time without supplemental oxygen; he recovered consciousness after eight hours, and at the end of a few weeks in the hospital showed no neurological damage as the result of this severe prolonged exposure. Von Tavel (5) reported two cases of severe collapse with unconsciousness lasting twenty-five minutes occurring at 24,300 feet in which no permanent damage resulted.

It would appear, therefore, that although the central nervous system is markedly affected by oxygen deficit (see below), survival unimpaired may be expected from even severe anoxia if the circulation is maintained. Oster, for example, found that the six animals which died during his experiments, all succumbed to anoxic anoxia superimposed on circulatory failure.

From the practical aspect of increasing an aviator's ability to withstand oxygen deprivation, very little has been learned during the past year despite many experimental attempts. Nor does it appear to the reviewers that much can be expected in this regard. It is unlikely that anything will be found which will magically increase tolerance to anoxia, and a more profitable approach is the current development of such devices as pressure-breathing, closed-cabin airplanes, etc.

The relation of resistance to anoxia to the effect of thiourea (12), thiouracil (13), dilantin (14, 15), cold (16), thyroxin (17), dinitrophenol (17), dextrose (18, 19), age (20), vitamin-B complex (21), carrot diet (22, 23), artificial polycythemia (23), yohimbin and calcium (24), irradiation of blood (25), insulin (19), epinephrine (19), monoiodacetic acid (19), and pituitary (19), has been investigated. These are discussed in the section on respiration in this volume.

The addition of carbon dioxide to oxygen mixture has been proposed as a method of increasing altitude tolerance (26, 27, 28). Carbon dioxide may produce benefit by: (*a*) dilatation of cerebral blood vessels; (*b*) increased blood pressure and minute volume of respiration; (*c*) shift in the dissociation curve of oxyhemoglobin to the right. From the practical point of view, however, increase in minute volume of respiration produced by carbon dioxide added to oxygen cannot increase alveolar oxygen tension and will decrease it by reason of displacement of oxygen by carbon dioxide. The increased effort associated with the hyperpnea increases oxygen consumption, and the heightened ventilation greatly increases

the amount of oxygen which must be carried in an airplane. It is doubtful whether an increase in cerebral circulation would more than compensate for all these factors. The addition of carbon dioxide while breathing air instead of oxygen will enable subjects to reach a higher ceiling since the increased depth of respiration in this case can improve alveolar and arterial oxygenation as indicated by the experiments of Gibbs *et al.* (26).

Welsh & Hyde (29) feel that resistance to anoxia is related to the acetylcholine content of the tissue under consideration. Thus, the order of increasing resistance of the central nervous system to anoxia is essentially the same as the order of increasing amounts of acetylcholine. The cerebellum and cortex have a low choline content, and are least resistant. Spinal nerves and autonomic ganglia have a higher acetylcholine content and are more resistant, while myenteric plexus cells which can resist complete anemia for three hours have an extremely high acetylcholine level (400 to 800 micrograms per gram).

Alterations in cerebral metabolism have been studied by Gurdjian and co-workers (30). Cerebral lactic acid rose when the oxygen content of the inspired air fell to a critical level of 11 to 13 per cent. As the oxygen percentage further decreased to a critical level of 7 per cent, decomposition of phosphocreatine was noted. In these anesthetized dogs no change in cerebral adenosinetriphosphate was detected at the degree of anoxia tested. A return to room air was followed by an extremely rapid resynthesis of phosphocreatine, but the lactic acid levels fell much more slowly (forty-six minutes after exposure to 4.2 per cent oxygen).

Much work has been done on the relation of adrenal cortical hormones to anoxia. Pincus & Hoagland (31) noted a hypersecretion of 17-ketosteroid in men at simulated altitudes and during the stress of actual flying, and feel that the chronic fatigue of pilots may be related to depletion of adrenal cortical hormones. Darrow & Sarason (32) have demonstrated such a depletion in anoxic rats. No evidence of altered adrenal function, however, was detected in a study of twenty-one commercial airline pilots, using the Wilder test, glucose tolerance test, and excretion of ketosteroids (33). The problem remains unsettled, although at least some of the changes in adrenal function, formerly attributed directly to oxygen lack, appear to be due to the concomitant diminution in carbon dioxide tension (34).

General effects of anoxia.—The respiratory response of eleven individuals to inhalation of 4.2, 5.2, and 6.0 per cent oxygen was measured by Horvath *et al.* (10). The general trend during the first five minutes of anoxia was upwards, reaching on the average (4.2 per cent oxygen) thirty liters per minute. The respiratory response was strong and sustained and in no instance dropped below the control level. Wide individual responses were noted, ranging from six to sixty-five liters per minute with 4.2 per cent oxygen. A striking feature of the recovery period was the slow decline towards normal breathing. Following sudden access to air of normal composition, breathing usually continued above the control level for from one to five minutes. It would have been interesting to know the effects of shifting to 100 per cent oxygen instead of to room air, since Smedal (35) reports apnea or severe respiratory depression following the administration of high oxygen concentrations to severely anoxic individuals. Associated with the increased pulmonary ventilation were a decreased arterial carbon dioxide content and tension (20.2 to 31.3 mm. Hg) and an increased alkalinity, the pH often reaching 7.6.

Graybiel (36) and von Tavel (5) report a change in blood pressure which has not commonly been associated with anoxia, stating that the diastolic pressure tends to decrease, as systolic levels rise. That this change may be significant is suggested by the work of Abramson which indicates a small, but definite increase in the rate of blood flow through the leg and forearm of normal individuals breathing ten per cent oxygen (37). The circulatory response to anoxia is thus similar to that following the subcutaneous injection of epinephrine, the characteristic finding in each instance being cardiac stimulation with a decreased average peripheral resistance.

Von Tavel analyzed the circulatory reactions just prior to the collapse of pilots at high altitudes (5). Such individuals showed a marked decrease in diastolic pressure, following by a drop in systolic pressure and a marked slowing of the pulse. This bradycardia has also been noted in normal individuals who assume the erect posture after being bled 500 to 1,000 cc. (38). Cerebral anoxia exists in both instances. Von Tavel believes the mechanism to be a protective one, tending to guarantee cerebral blood supply by enforcing the horizontal position (fainting) as well as conserving oxygen through unconsciousness and immobility.

Of 2,798 men exposed to a simulated altitude of 18,000 feet

without oxygen for fourteen to sixteen minutes, 6.5 per cent developed marked syncopal reactions, 0.9 per cent losing consciousness (39). Electroencephalographic studies were made in ten of these "fainters." They revealed patterns similar to those seen in epilepsy in seven. The syncopal reactions might be the result of hyperventilation and alkalosis in susceptible individuals (30, 26). The suggestion has been made that impulses from the carotid and aortic bodies may reflexly maintain cortical function in the face of anoxia (41). Syncope might therefore result in those individuals who show little evidence of chemoreceptor stimulation in response to anoxia (42). Evidence bearing on this has been obtained by Randall in dogs (43).

In an excellent review of the effects of anoxia on the eye, Weaver (44) points out the various alterations in ocular function which have been observed. These include reduction in visual acuity, size of visual fields, color vision, and speed of dark adaptation. He notes that latent deviation or imbalance of extraocular muscles may become manifest under oxygen lack, and diplopia may appear. McFarland (45) has measured the latency of the "tertiary" visual after-image, and found that anoxia prolongs this. This effect is consistent with the apparent dimming of the visual field noted above. He also made the interesting observation that inhalation of oxygen produces only a slow recovery of this function. Since the retina embryologically is part of the central nervous system and resembles it, metabolically and anatomically, this slow recovery may indicate a similar slow recovery in the central nervous system after anoxia.

Alterations in behavior have been frequently noted as accompanying anoxia, and a comparison with acute alcoholism is often made. Barach (46, 47) has made further observations on the impairment of emotional control caused by anoxia, and believes that this change is a reliable index for pilot selection. The affective response may be depressive in nature, or may take the form of exhilaration, the mood varying with the nature of the individual. Von Tavel (5) noted a predominantly euphoric reaction in only 10 to 20 per cent of his subjects, while Barach found euphoria in 50 per cent and dullness in 50 per cent of a smaller series. It appears that the capacity to control one's emotions is acutely dependent on the maintenance of an accustomed oxygen tension in the brain.

Neutrophilic leucocytosis (48), certain changes in blood sugar levels (49), and diminished volume of urine associated with anoxia (50) can all be attributed to increased sympathetic activity. Perhaps the effects of anoxia on the intestinal tract reported by Van Liere (51, 52, 53) are likewise related.

Oxygen Toxicity

Becker-Freyseng & Clamann (54) exposed themselves to 90 per cent oxygen at 760 mm. Hg total pressure continuously for sixty-five hours. In both subjects a diminished vital capacity was observed together with a rise in temperature in one individual. (The possibility that part of this response is due to absorption of alveolar oxygen with subsequent atelectasis should be considered.) Abnormal sensations (prickling and dullness) were noted in hands and feet, and in the absence of signs of neurological disorder, one wonders if these were the result of vasoconstriction caused by the oxygen (55). These workers have repeated their work, exposing themselves to 82 per cent oxygen for seventy hours at a total pressure of 230 mm. Hg; no changes in their well-being were observed.

These results indicate (*a*) that man is much more resistant to high concentrations of oxygen than are small animals but that damage may occur; (*b*) that an increased percentage of oxygen is harmless even if inhaled for days provided that the partial pressure is normal.

Friederich & Grayzel (56) have observed rhesus monkeys exposed continuously to 90 to 95 per cent oxygen. Ten animals were studied and two survived twenty days of continuous exposure. The earliest signs of toxicity noted were cough and dyspnea (third to fifth day) and anorexia (fourth to fifth day). The first animal died on the sixth day.

Concentrations of oxygen approximating 100 per cent were administered to patients with sickle cell anemia, and depression of erythropoiesis was observed (57). This effect may be the physiological antithesis of the erythroid stimulation produced by low oxygen tensions. Although the administration was allegedly "without intermission for eight to twenty days" the results do not bear particularly on the problem of oxygen toxicity, since the authors admit intermittency of exposure due to eating, talking, and part time wearing of a nasal mask.

Oxygen administered under pressure greater than one atmos-

phere produces toxic symptoms primarily of the central nervous system. Bean exposed rats to 100 per cent oxygen at sixty-five pounds pressure (4.4 atmospheres) and noted no effect on maze learning but definite impairment of retention and memory (58). Williams & Beecher (59) in a study of the effect of oxygen at one to ten atmospheres on *Drosophila* report that toxicity increases directly with the temperature, and inversely with age. It is interesting to note that since *Drosophila* do not possess respiratory blood pigments, an increase in carbon dioxide tension is not essential to the development of oxygen poisoning (59).

Many theories have been advanced as to the cause of oxygen poisoning. Most promising of these involves the action of oxygen upon enzyme systems of cells. In a comprehensive review, Stadie *et al.* (60) state

> the likelihood is increasing that the toxic action of high pressures of oxygen will be explained in the light of inhibitory actions on enzymes with resultant severe disturbances of essential metabolic cellular reaction. The evidence in the literature is scanty and non-systematized, but is sufficient to suggest the following possible modes of action of oxygen: (1) Oxidation of a coenzyme to the inactive oxidized form. (2) Oxidizing activating sulfhydryl compound. (3) Oxidizing active-SH groups of enzyme molecule proper. (4) Oxidation of metallo-hemochromogen to inactive oxidized form. (5) Oxidizing activating metal constituent. (6) Formation of inhibitor from precursor other than the enzyme. (7) Inhibition of enzymatic activity by changing oxidation-reduction potentials of medium.

Effects of Decompression

Bends.—Radiological evidence of aseptic bone necrosis occurring in caisson workers (61, 62) indicates that there is some interference with blood supply to bone. This may be due to the pressure exerted by nitrogen bubbles in the medullary cavity or under the periosteum, or to arteriolar gas emboli in the epiphyseal or metaphyseal area where anastomoses are limited. Formation of gas emboli, which should be rapidly absorbed, scarcely explains the long lasting changes following temporary decompression sickness; one wonders whether the introduction of gas bubbles into arterioles may lead to fibrin and thrombus formation. Similar bone changes were not seen in aviation personnel who have experienced bends.

MacKenzie & Riesen (63) have exposed eighteen subjects for approximately two hours to simulated altitudes of 25,000 to 30,000 feet on three to five different occasions; mild exercises were per-

formed every ten minutes. Under these circumstances, severe bends occurred in three subjects at 26,000 feet, in five at 27,000 feet, and in eight at 28,000 feet. The authors felt that bends susceptibility or resistance might be determined on the basis of the presence or absence of bends in the first two ascents. Examination of their data indicates that such a test might be accurate for those highly resistant or highly susceptible to bends but would be unreliable for a large middle group. Certainly a statistical analysis of much larger groups subjected to more flights at different altitudes must be done before pilot selection can be carried out on this basis.

Syncope.—Romano *et al.* (64) observed ninety-one instances of syncope occurring at a simulated altitude of 35,000 feet in individuals with normal arterial oxygen saturation. The reactions were usually characterized by hypotension, bradycardia, faintness, dizziness, pallor, nausea, and sweating and were preceded by symptoms of bends or chokes in most instances. It is difficult to determine whether the syncope was of psychic origin (threatening situations) or was of true reflex origin. Arterial puncture is often followed by similar collapse (65) and it is possible that distention of endarteries by expanding gas in cases of bends may produce this type of response. If this is a specific reflex, it is probably limited to the unanesthetized state, for mechanical manipulation of arteries other than the carotid sinus does not lead to hypotension in anesthetized animals; in fact, chemical stimulation of arterioles leads to a reflex increase in blood pressure and acceleration of the pulse (66). The fact that similar collapse has been noted following a wide variety of stimuli (arterial puncture, venipuncture, distention of the duodenum or rectum) strengthens the belief that it is a nonspecific reaction to afferent impulses (67).

Another response noted at a simulated altitude of 35,000 feet in well oxygenated individuals has been a migraine-like syndrome which occurred in seventeen of one hundred fifteen subjects (68). Aeroembolism of cerebral vessels may be involved in its causation, rather than the cerebral vasoconstriction suggested by the author; the latter is unlikely since oxygen tension is normal when breathing 100 per cent oxygen at this altitude.

Expansion of gases.—Peterson *et al.* have exposed two patients with artificial pneumothorax to reduced pressures and as expected were able to produce 75 and 90 per cent collapse of the affected

lung (69). In the latter case, oxygen saturation dropped from 100 to 90 per cent despite oxygen inhalation. They emphasize that cases with pneumothorax (traumatic or artificial) should not be transported unless provision for aspiration has been made prior to or during flight. Patients with paralytic ileus, gut perforations, or with abdominal wall incisions must be transported at low altitudes (70). Experiences with aerial transport have been recorded by Tillisch *et al.* (71).

Effects of decompression upon the middle ear (72) and upon the teeth (73) have been reported.

Airsickness

Campbell (74) has summarized the problems of airsickness indicating that such disturbances must be considered from a variety of viewpoints, including vestibular function, optical illusions, movements of viscera, psyche, sensations from muscles and joints, influence of endocrine glands, and changes in the gastrointestinal tract. The majority of writers (75, 76) appear to believe that airsickness is a neurosis, although an increased incidence is noted in association with hot weather, gas forming foods, and fatigue (77).

From the standpoint of treatment scopolamine (hyoscine) has been advocated by two investigators (78, 79), who also feel that such medication is helpful in minimizing seasickness. Pavatrine (β-diethyl aminoethyl fluorence-9 carboxylate hydrochloride) has been used with some success also, according to Davidson (80), who has determined that this drug can safely be given to aviators subjected to anoxia or high altitudes.

INDUSTRIAL AND MILITARY FITNESS

A major problem in wartime is the evaluation of a man's fitness for proper performance of industrial or military duties, the effect of environment, nutrition, and fatigue upon his performance, and the use of measures designed to improve performance. Fitness tests have been reviewed by Taylor & Brozek (81); emphasis has been placed upon the desirability of rigid standardization of tests and test conditions so that data from different laboratories dealing with the effects of anoxia, fatigue, heat, cold, diet, etc. upon performance may be compared. This is important now that the field of physical medicine is expanding rapidly under the impact of

convalescent and rehabilitation problems created by the war (1, 82).

Fitness tests.—The results of fitness tests may be influenced by the amount of pretest exercise, sleep and food, the emotional state, motivation factors, temperature, and relative humidity. When performance tests of the psychomotor coordination type are used it is desirable that they mimic the conditions under consideration [manipulation of flying controls (83) or of Link Trainer for aviation cadets, or automobile driving test for truck drivers]. However if large groups of subjects are to be tested, the tests must be simple ones, involving little skill, learning, and fatigue. Whenever possible objective measurements should be made such as those in tapping, code, or flicker fusion tests. More complex tests, such as pursuit meters (31, 84) may be used if more sensitive tests are required. However in these, learning is prolonged and considerable time must be spent in reaching a plateau; this limits the number of subjects severely. Tests must be of long duration to prevent brief spurting as an important factor but short enough to prevent muscular fatigue. Patterns must be so erratic as to prevent anticipation.

If motor tests are to be employed, maximal effort ("to exhaustion") is preferable to submaximal, in that the former places all subjects, fit or unfit, under a severe strain but it involves cooperation and motivation on the part of the subject (85). Treadmill exercise is the easiest to standardize and involves little learning or special muscle groups, but the bicycle and step tests (86) are often more convenient to use and give reproducible results. The latter has proved to be useful in selection of combat officers (87). The Schneider test is now believed to be of low reliability (88).

Postexercise heart rate and blood lactate proved to be the most reliable measures of submaximal work, while time run and postexercise heart rate were most reliable for maximal work (85, 89). Respiratory rate and volume, oxygen consumption, expired air oxygen and carbon dioxide concentration, and respiratory efficiency may also be measured. Changes in palmar skin resistance (90), due to increased sweating caused by sympathetic stimulation, appear to be unreliable as a fitness test in view of the many factors found to influence the chloride concentration in sweat (91). The use of the postexercise differential blood count as an indication of physical fitness requires further study (92). Circulatory fitness

may be tested by tilting, exercise, or by the Flack test (81, 93, 94).

There is a decided advantage in employing a battery of coordination, motor, and intelligence tests if fatigue does not result and if time is permitted for multiple tests. The latter is important in testing anoxic individuals since deterioration is a function of time as well as of the degree of anoxia.

Performance tests have been used chiefly in evaluating the effects of diet, drugs, anoxia, and fatigue.

Diet and performance.—The thiamine requirement of man has been defined as the amount needed to allow the maximal and most efficient performance of the body (95). It is possible that the computation of thiamine requirements for man on the basis of those determined for rats or dogs may be grossly incorrect (95) and consequently numerous attempts have been made to determine the minimum daily amount of thiamine which will permit no detectable deterioration of performance in man. This is a matter of great importance, for according to the existing standards, a large percentage of the American population has been existing on a thiamine-deficient diet for many years (96, 97, 98).

In a series of carefully controlled studies involving a battery of thirteen tests and rigid standardization of all conditions, Keys *et al.* (95, 99, 100) have concluded that 0.23 mg. of thiamine per 1,000 calories daily for a three month period is an adequate amount even during severe exercise. Whether this figure may be reduced further has not been investigated by this group though Najjar & Holt (101) believe that a daily intake of 0.15 mg. per 1,000 calories may be compatible with health. This indicates that the thiamine requirement set by the National Research Council is considerably too high, even with reasonable allowances for a margin of safety. The alternate conclusion is that the performance tests employed are not sensitive enough to detect the small changes that might conceivably occur with a slightly deficient diet. It would be interesting to know the magnitude of change that would occur in individuals subjected to severe enough thiamine lack to cause a clinically recognizable deficiency state.

The work of Keys *et al.* has been disputed by Barborka, Foltz & Ivy (102) whose experiments purported to show decrease in work performance of individuals with a "deficient" diet containing 0.65 mg. thiamine per day and an increase when large amounts of thiamine were restored to the diet. Actually the data of only one

of the four subjects was presented and it is significant that the vitamin deficient diet was given during the hot months of June, July, and August while the high vitamin diet was begun in September. Furthermore no control subjects were used and only one type of test was used to judge performance. The experiments of Frankau (103) and Fishbein *et al.* (104) dealing with improvement in performance following administration of B-complex again were not adequately controlled in contrast to the work of Keys *et al.* The beneficial effects of B-complex and pantothenate upon the work output of perfused frog muscles (105, 106) obviously bears no relation to the quantitative determination of vitamin requirements of man.

Pitts *et al.* (107) have shown that the dietary protein may vary widely (75 to 150 gm. per day) without any noticeable effect upon performance of intermittent work, in either temperate or tropical conditions. This refutes the older concept that a high protein diet places a load upon the heat dissipating mechanisms because of the high specific dynamic action of protein.

The importance of adequate salt intake in maintaining performance in hot environments has been stressed by Taylor *et al.* (108). Experimental evidence has been presented to show that thiamine and vitamin-K requirements are higher in tropical heat (109, 110).

Drugs and performance.—Pincus & Hoagland (111) have reported improvement in performance scores upon the Stevens serial coordination meter and the Hoagland Werthessen pursuit meter of subjects given 50 mg. of pregnenolone daily. Improvement occurred slowly over a period of seven to ten days and fell off when placebos were substituted. No improvement followed the administration of adrenal cortical extract or of progesterone. It was believed that replacement of certain ketosteriods, excreted in excess during periods of fatigue, was responsible for the improved performance, though metabolic effects such as nitrogen retention should be considered as a factor. Despite the authors' statement that pregnenolone is completely nontoxic, careful studies of the effect of prolonged administration upon sex functions should be carried out.

Simonson found that desoxyephedrine and amphetamine increase the fusion frequency of flicker and relieve fatigue (112). These drugs should be reserved for emergency use for periods of

excessive stimulation might well be followed by fatigue of the central nervous system.

Price & Pedulla (113) found that sulfadiazine administration produced no alteration in reaction time or coordination but in our experience the test used ("Drivemobile") is so insensitive that no deterioration could be detected in subjects breathing 10 per cent oxygen.

Anoxia and performance.—Foltz & Ivy (114) using the double work period technique found no decrease in performance of medical students subjected to simulated altitudes of 10,000 feet or 15,000 feet for one hour. Upon exposure to 18,000 feet for one hour, three of the four showed some decline in work output.

It should be pointed out that pilot selection involves considerably more than the ability to perform well while anoxic for only a very small percentage of pilots may be exposed to altitudes at which anoxia will occur despite inhalation of 100 per cent oxygen.

Fatigue and performance.—Foltz *et al.* (115) found no significant correlation between subjective estimation of well being and work output. However, when a group of truck drivers were subjected to a battery of motor and coordination tests, a definite correlation with subjective fatigue was shown. Simonson reported a falling off in flicker fusion frequency with fatigue (112), while Graybiel obtained opposite results (116). These studies are representative of the confusion existing in this field.

The comprehensive study of fatigue in truck drivers by Jones, Flinn & Hammond (117) is an example of the intensive type of investigation required to yield conclusions of value. In all, 889 drivers were examined in 1,200 test sessions and subjected to a large variety of performance and nonperformance tests. The four functions which showed the closest relation with hours of driving were speed of tapping, simple reaction time, reaction coordination time, and manual steadiness.

In summary, it appears to the reviewers that the measurement of man's performance and of the effects of diet, drugs, and anoxia upon it represents one of the most difficult of all investigative tasks, and one that requires a full-time staff, full-time subjects, and the most rigorous controls of both tests and environment. Yet innumerable physiologists, though conscientiously attempting to unravel problems directly connected with the wartime needs of the armed services, have measured man's performance in relation

to new environments without full appreciation of this concept. Consequently many of these studies have already required, or will require, reinvestigation by those more fully aware of the innumerable difficulties peculiar to this field.

RESUSCITATION

Resuscitation is a problem of importance at the present time for several reasons: (*a*) great numbers of individuals are being exposed to the hazard of drowning in wartime, particularly in amphibious operations; (*b*) the increasing use of intravenous barbiturate (pentothal) anesthesia has been accompanied by many instances (118) of profound depression of vital functions; (*c*) new methods of resuscitation have been introduced. This review will evaluate techniques of resuscitation from two points of view: practicality and efficiency.

Practicality.—Drinker (119) has emphasized that the most important consideration in choice of methods is the speed with which each can be brought into effective use. The chances of resuscitating an individual with primary respiratory failure (with the circulation still active) are 100 per cent if respiration has just ceased, 97 per cent if respiration has stopped for one minute, 92 per cent if stopped for two minutes, 75 per cent if stopped for three minutes, 50 per cent if stopped for four minutes, and 25 per cent if stopped for five minutes.

Immediate availability is the virtue of the simple measures advocated by Waters (120). These include mouth to mouth insufflation, or, for disasters occurring in operating rooms, pressure on the rebreathing bag, preferably modified with a safety valve set at 14 mm. Hg (121). A simple hand bellows devised by Kreiselman (122) may be used; it is compact, portable, light (2 lbs.), and contains safety valves to prevent excess pressures. Finally, the Schafer or Silvester techniques can also be speedily applied. Since the chances of revival fall off sharply after the second minute, Henderson was justified in his crusade against mechanical devices which are rarely available when the emergency arises (123, 124).

Efficiency.—Cordier (125) has summarized experimental evidence on the amount of ventilation obtained with the Schafer and Silvester methods. If the nonrigid cadaver is used as the test object the Silvester method is far superior (the tidal air being 200 cc. to 20 to 50 cc.). This is presumably because the Silvester method

actively expands the chest to produce inspiration. The Schafer method produces active expiration and depends partly upon the elastic recoil of the chest and abdomen for inspiration and in the cadaver these structures have lost their elasticity and tone. When normal subjects who have voluntarily suspended their respiration are used as test subjects, there is no agreement whatever concerning the relative efficacy of these techniques (lung ventilation with Schafer's method varied from 350 to 1000 cc. and with Silvester's from 178 to 2000). This confirms the impression of Henderson & Turner (124) that in normal individuals respiration is governed over a period of minutes by the carbon dioxide tension of arterial blood and automatically regulates itself to normal levels despite vigorous manipulations; the results obtained upon such subjects therefore are completely undependable.

Ideal test objects are subjects in whom artificial respiration is urgently required, such as patients apneic because of an overdose of narcotic agents. In view of the prolonged controversy in this field, it is amazing to note that only two investigators have used such material. Waters & Bennett (126) anesthetized patients to the point of respiratory failure and noted a superiority in the Silvester method over the Schafer method (214 cc. vs. 180 cc. in two women and 933 vs. 662 cc. in two men); MacIntosh (127), in a similar experiment, also noted its superiority (400 vs. 340 cc.). However in both these studies, the apnea was produced by hyperventilating the anesthetized subjects; this certainly reduced the arterial carbon dioxide tension and so put the Schafer method at a disadvantage. In general, however both methods can be counted upon to produce ventilation adequate for the reduced oxygen need of anesthetized or comatose patient.

Eve has recently proposed a new approach to resuscitation utilizing diaphragmatic movements in his gravity or rocking method (128 to 131). The patient is tied on to a stretcher, door, ladder etc. and a fulcrum is provided (trestle, etc). (The Sanders oscillating bed might be useful in hospital practice.) He is rocked through a 45° angle up and then down at a rate of 10 to 12 cycles per min. In the head down position the abdominal organs slide against the diaphragm and produce expiration; in the head up position these organs go feetward, pull down the diaphragm, and so produce inspiration. The diaphragm thus acts as a piston in the thorax. Roentgen pictures have shown a five centimeter excursion

of the diaphragm during rocking (128). In normal subjects with voluntarily suspended respiration the Eve method has produced tidal airs of 1500 cc. (128), 900, 900, 1500, 325, 700, 600 cc. (132), and 400 to 830 cc. (129). When employed in deeply anesthetized individuals who were overventilated so as to produce apnea, the Eve method resulted in a tidal air of 150 cc. (Schafer, 160 cc.) in one case (126) and 580 cc. (Schafer, 340 cc.) in another (127). Hemingway & Neil have compared the Eve method with a "supine pressure" method in anesthetized dogs made apneic by cervical cordotomy or by overdose of pentobarbital; rocking at a rate of 8 to 10 per min. produced a volume tidal air 54 per cent greater than the modified Schafer method (eleven experiments); in some instances the tidal air was more than doubled using the rocking technique.

The Eve method of resuscitation not only provides artificial respiration but also exerts beneficial effects upon the circulation. Cardiac output measured by the direct Fick principle in dogs was 25 per cent greater with rocking than with the abdominal pressure method (133). Cerebral circulation and coronary circulation may be improved to an even greater degree by the rocking technique (131, 133); in the head down position a column of blood approximately three to four feet long would supply the coronary and cerebral vessels with blood at a pressure of 66 to 88 mm. Hg (131). The tilting method may involve augmentation of carotid sinus pressure receptor reflexes though the cycle is probably too rapid to permit full activation of the sympathetic vasoconstrictors concerned.

Conspicious success has been achieved with Eve's method, even in small boats at sea (134). It is simple, involves little energy and produces little fatigue on the part of the operator. It may be carried out by unskilled hands without fear of harming the patient, even if his ribs have been fractured, and is effective even if the thoracic muscles have lost their elasticity and tone (134).

However the Schafer, Silvester, or mouth-to-mouth technique must be employed continuously up to the moment of actual rocking (134). Furthermore the operator must be cautioned against rocking too rapidly, for overventilation, with a decreased arterial carbon dioxide tension, may result. Nathan, (132) using normal men, noted an increased ventilation up to 20.5 L per min. with a rate of 13 per min. (the tidal air being 1500 cc.). Hemingway &

Neil observed that the minute volume of respiration in dogs more than doubled when a rocking rate of 16 per min. was used. They advised that the rate of rocking should not exceed 10 cycles per min.; the optimal angle was found to be 45° in these animals.

Motion sickness induced by the cyclic tilting is said to be an insignificant factor (134); it would be bothersome only in conscious patients with respiratory failure (i.e., poliomyelitis cases).

The effect of tilting upon cerebral and coronary circulation when normal heart action has ceased has not been adequately studied. The cause of the hyperpnea often induced by tilting normal unanesthetized persons and the effects of prolonged tilting upon the abdominal viscera should be investigated.

Suck and blow resuscitators have been designed to inflate the lungs rhythmically under a positive pressure up to 14 mm. Hg, the expiratory phase being accomplished by suction not exceeding 8 mm. Hg. Henderson in his last publication before his death (123) opposed these resuscitators for the following reasons: (*a*) The inspiratory cycle ceases when a certain pressure is attained in the respiratory tract. This pressure may be reached before sufficient volume has been delivered in cases of obstruction in the upper respiratory tract (by mucus, relaxed pharynx, or tongue) or when the patient's own insufficient respiration is out of phase with the pump. Under such circumstances anoxia may result. (*b*) Under certain circumstances the combination of pressure and suction may lead to hyperventilation and acapnia which in turn may lead to a fall in blood pressure, especially in narcotized individuals (135, 137). In addition Drinker states that positive pressure does not ventilate the lungs as evenly as normal respiration; with the former, air is distributed chiefly to the most easily expanded portions of the lung and the posterior portions become atelectatic and edematous (119).

The amount of positive pressure required to rupture alveoli has never been satisfactorily determined. Polak & Adams (136) found that approximately 80 mm. Hg. pressure was required to produce lung rupture in dogs, but Marcotte *et al.* (137) found that intrabronchial pressures in excess of 24 mg. Hg. routinely ruptured alveoli. The former employed short periods of inflation (10 sec.) and used the appearance of bubbles in a carotid trap as their endpoint; the latter employed long, continuous periods of inflation (18 to 75 min.) and used the gross presence of air along the great vessels

at the hilum of the lung as their criterion of rupture. A species difference also appears to exist, since mediastinal emphysema followed the use of only 16 to 20 mm. Hg. intrabronchially in cats (137). Rasmussen & Adams (138), using intermittent intrabronchial pressures of 20 to 50 mm. Hg. at a rate of 28 per min. for 15 min. twice a week for as long as eleven months in dogs, observed acute death following 45 to 50 mm. Hg. pressure, and mediastinal emphysema following pressures of 20 to 35 mm. Hg. Obviously more experiments are required upon normal and diseased lungs to settle this point. These should simulate the actual conditions existing during suck and blow resuscitation and should include careful gross and microscopic examination of the lungs.

Suction during expiration may stimulate the respiratory center reflexly over the vagus nerves by producing more complete alveolar collapse; this is probably the basis of the phenomenon of "asphyxial resuscitation" (139, 140). Suction during expiration may be used to stimulate depressed respiration, but should be discontinued if it fails in this regard. A moderate weight applied to the chest wall will probably serve as well without incurring the risks involved with suction. The production of expiration by suction (rather than by passive collapse of the distended lungs and chest) has been claimed to remove noxious gases from the alveoli more rapidly than by normal respiration (141). This is questionable unless simultaneous hyperventilation is produced and the resulting acapnia might well result in harm.

In view of the widespread use of resuscitators it is interesting to note how few experiments have been reported in support or condemnation of them. Coryllos performed experiments upon six dogs using a resuscitator: three dogs died after the application of the resuscitator for one to six hours; three others, on whom body temperature was maintained by heating pads or by warming of the inspired air, lived (142). Ross' study of resuscitation in human asphyxia served chiefly to emphasize that mechanical resuscitators are used more than all other methods combined (143). The experiments of Steinberg & Dietz (144) are of little value since no information was given regarding circulation at the time of resuscitation. It appears to the reviewers that impartial investigations should be made of the physiological and pathological effects of suck and blow resuscitators upon the respiratory and circulatory systems.

Draper & Whitehead (145) have commented upon the possibility of diffusion respiration occurring in apneic dogs; with all respiratory movements abolished a dog consumed an average of 108 cc. of oxygen per minute over an eleven minute period (normal, 145 cc.). Possibly diaphragmatic flutter, vigorous cardiac contractions, ciliary action (146), or carbon dioxide absorption by soda lime caused some movement of air. At any rate it would appear to be risky to depend upon this to the extent of supplying oxygen by mouth catheter and abandoning the use of chest movements.

Fisher (147) has reviewed methods of resuscitation from the earliest barbarian attempts down to the present era of mechanical resuscitators. Many of the earlier seemingly crude methods may now be classified on a physiological basis: respiratory stimulation due to (*a*) sensory nerve stimulation, i.e., cutting or burning of the skin, dilatation of the anal sphincter, flagellation, friction, cold, pulling of teeth, etc.; (*b*) joint proprioceptor stimulation, agitation, shaking, pulling, walking about; (*c*) chemoreceptor stimulation, injection of tobacco smoke (nicotine) into lungs or rectum; (*d*) increase in cerebral circulation by inversion; (*e*) Hering-Breuer reflexes (suction to lungs). Similarly reduction in oxygen consumption may have been partly the basis for the success attendant upon packing patients in ice or snow.

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PHARMACOLOGY

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With the approval of the Editorial Committee, several topics of current interest will be discussed in this section, instead of a single subject as set forth in earlier volumes of this journal.

THE DIGITALIS GROUP

The last two decades have witnessed important developments in this field since the publication of Cushny's monograph (1). While a comprehensive review will not be attempted, a few phases of its progress may be treated briefly here.

Classification of active principles.—The cardiac action of digitalis is shared by substances in several other plants and in the venom of toads (family, Bufonidae). With few exceptions, the active principles have been isolated in crystalline form, as previously surveyed by Jacobs (2) and Elderfield (3). Table I summarizes all the information to date. The references cited are not necessarily the first papers in appearance. Their selection depends upon the substantial information they offer. The potency figures in cats, as expressed by the geometric means of lethal doses, namely, the antilogarithms of the means of logarithms of individual doses, have been determined by a uniform technique in the reviewer's laboratory; this affords a homogeneous scale of comparison. In a few instances, they have been recalculated from the original crude data. There are four classes of compounds. The plant substances readily fall into two classes—the glycosides and the *Erythrophleum* alkaloids.

Glycosides.—These substances are conjugation products of sugars and of non-sugar parts known as aglycones. The list in Table 1 does not include cortenerin of *Nerium oleander* (47), somalin of *Adenium somalense* (48), ψ-tanghinin of *Tanghinia venenifera* (49), and helleborin of *Helleborus niger* (50). The glycosides may be subdivided into monosides, biosides, triosides, etc., depending on the number of molecules of a sugar or sugars attached to the aglycone molecule.

Erythrophleum alkaloids.—These are organic bases occurring in *Erythrophleum* species. They easily form water-soluble salts with inorganic acids. Uscharin contains both nitrogen and sulfur, but does not appear to be a typical alkaloid (25). Rather, it corresponds to a glycoside after the splitting off of nitrogen and sulfur.

With one exception, namely, *Bufo alvarius*, the poison of each species of toad yields two digitalis-like principles, which may be named generically bufagins and bufotoxins.

Bufagins.—These substances resemble chemically aglycones, and in name are prefixed by appropriate terms relating to the species of toad. Wieland's bufotalin (41) properly belongs to this class.

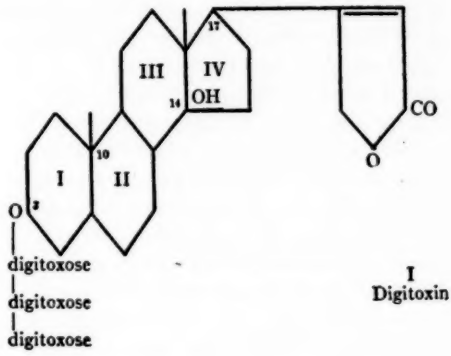
Bufotoxins.—These are conjugation products of specific bufagins and suberyl-arginine. They are not alkaloids because the nitrogen arises from the arginine part of the molecule rather than from the ring nucleus.

Qualitatively, all four of the above classes, in appropriate doses, have the same pattern of cardiac action: systolic standstill on the amphibian heart; and bradycardia, P-R prolongation, inversion of T-wave, ectopic rhythm, secondary tachycardia, and ventricular fibrillation on the electrocardiogram of the intact mammalian heart. In addition, they all cause nausea and emesis in pigeons and cats due to stimulation of the vomiting center, and, in large doses, a rise of arterial blood pressure due to peripheral vasoconstriction. They are also known to contract isolated rabbit intestine and guinea pig uterus due to direct stimulation of the smooth muscles of these organs.

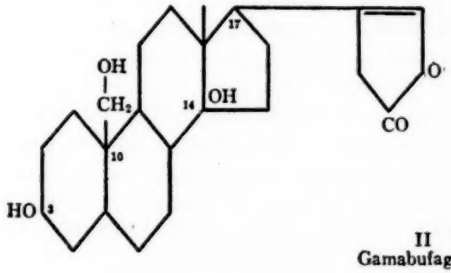
There are quantitative differences, individually, among these potent substances. Thus, the majority of them, when injected intravenously, have a more prompt action than digitoxin and oleandrin (also known as folinerin) (17, 51). The two latter, however, have a marked persistence of action, lasting for many hours. Solubility is no indication of easy absorption from the gastrointestinal tract. For example, ouabain and cymarin, though very soluble in water, are notoriously unreliable in their effects when given by mouth, while digitoxin, although less soluble, is completely absorbed following oral administration (52). It has also been shown that the emetic and cardiac actions do not run parallel (51).

Functional Groupings in the Molecules of Cardiac Substances

Glycosides, bufagins, and bufotoxins all contain a steroid ring system with an unsaturated lactone ring on C_{17}, as, for example, digitoxin (3) and gamabufagin (53, 54) shown in Formula I and Formula II, respectively.



I
Digitoxin



II
Gamabufagin

The similarity of chemical structure undoubtedly accounts for the identity in pharmacological action of the principles, though they occur in various plants and toads that are not phylogenetically related to one another. Repeated investigations in animals with a few selected compounds reveal that certain parts of the molecule are necessary for the preservation or enhancement of the cardiac action. They may be treated as follows:

(*a*) ***The lactone ring.***—This is indispensable if the typical ac-

tion is to be retained. Equally important is the double bond in the lactone ring. Thus, either saturation with hydrogen, or rupture of the lactone ring by saponification, results in loss of cardiac action. Test examples have been made with digitoxin, ouabain, cymarin, cinobufagin, and marinobufagin (55 to 60). It is probable that the same point can also be demonstrated with other substances.

(*b*) ***The hydroxyl group on*** C_{14}.—For some unknown reason, this hydroxyl group is also indispensable. For example, its modification in the strophanthidin molecule (the aglycone of cymarin) to form isostrophanthidin is followed by loss of action (60). The same is observed with its disappearance in the molecules of α- and β-anhydrodigitoxigenins (61). The significance of this hydroxyl group will be dealt with further in a later section.

(*c*) ***The stereochemical arrangement.***—A change in stereochemical arrangement in the ring system has a remarkable influence on the pharmacological action of these substances. Thus, allocymarin and allostrophanthidin, though having an intact lactone ring and a double bond, are devoid of any digitalis-like effect on the heart (60, 62). It is possible that the hydroxyl group on C_{14} in the molecule of allostrophanthidin, and thus, of allocymarin, bears a *trans*-configuration with the aldehyde group on C_{10} and the side chain on C_{17} (63). For a similar but not identical reason, adynerin, a glycoside of ***Nerium oleander***, has been found to be inert (64). *Cis*- and *trans*-isomerisms are also responsible for the differences in potency of digitoxin, thevetin, and uzarin, the aglycones of which have the same formula, the *cis*-form of linkage of rings I and II being more active (65). Results so far reported indicate that both the unsaturated lactone ring and a favorable spatial isomerism in the steroid ring system contribute to the preservation of cardiac action of three classes of compounds—the glycosides, the bufagins, and the bufotoxins.

(*d*) ***The sugar component.***—All glycosides have one or more molecules of a sugar, or sugars, attached to their aglycones. The carbohydrate parts possess no cardiac activity themselves, but are capable of increasing the digitalis-like effect when coupled with the aglycones. In other words, the natural glycosides are more potent than their degradation products, the aglycones (66). A com-

TABLE I

Principles Having a Digitalis-like Action

Source	Parts Having Activity	Cardiac Principle	Mean (Geometric) Lethal Dose ± S. E. in Cats
			μg. per kg.
Digitalis purpurea	Leaves	Glycoside A (4)	469.2 ± 13.2 (5)
		Glycoside B (4)	548.4 ± 21.5 (5)
		Digitoxin (6)	325.3 ± 11.5 (7)
		Gitoxin (8)	indeterminable (5)
D. lanata	Leaves	Lanatoside A (9)	361.0 ± 17.2 (5)
		Lanatoside B (9)	387.8 ± 27.7 (5)
		Lanatoside C (9)	232.6 ± 18.1 (5)
		Deacetyl-lanatoside A (9)	469.2 ± 13.2 (5)
		Deacetyl-lanatoside B (9)	548.4 ± 21.5 (5)
		Deacetyl-lanatoside C (9)	unavailable
		Digitoxin (9)	325.3 ± 11.5 (7)
		Gitoxin (10)	indeterminable (7)
		Digoxin (10)	231.0 ± 9.3 (7)
Strophanthus kombé	Seeds	K-Strophanthoside (11)	186.5 ± 11.1 (12)
		K-Strophanthin-β (13)	128.2 ± 3.1 (12)
		Cymarin (13)	110.1 ± 3.7 (7, 14)
S. gratus	Seeds	Ouabain (15)	116.0 ± 2.7 (7)
S. sarmentosus	Seeds	Sarmentocymarin (16)	202.0 ± 11.3 (17)
S. eminii	Seeds	Emicymarin (18)	151.7 ± 8.4 (17)
Periploca graeca	Vine	Periplocin (19)	120.5 ± 6.0 (12)
		Periplocymarin (20)	153.9 ± 5.5 (12)
Convallaria majalis	Flowers	Convallotoxin (21)	79.0 ± 3.1 (7)
Scilla maritima	Bulbs	Scillaren A (22)	146.0 ± 10.1 (7)
Antiaris toxicaria	Milky juice	α-Antiarin (23)	116.4 ± 4.3 (17)
		β-Antiarin (23)	102.8 ± 3.3 (7)
Calotropis procera	Leaves and stems	Calotropin (24)	111.3 ± 3.1 (14)
C. procera and *gigantea*	Milky sap	Uscharin (25)	144.5 ± 9.3 (14)
		Calotoxin (25)	112.3 ± 10.6 (14)
Thevetia neriifolia and *ycotli*	Nuts	Thevetin (26)	889.0 ± 31.6 (27)
Cerbera odollam	Nuts	Cerberoside (28)	813.7 ± 78.0 (28)
		Cerberin (28)	147.0 ± 5.7 (28)
Nerium oleander	Leaves	Oleandrin (29)	197.1 ± 10.4 (27)
		Desacetyl-oleandrin (29)	300.2 ± 22.7 (30)
Gamphocarpus species	Woody parts	Uzarin (31)	4586 ± 737 (7)
Erythrophleum guineense	Bark	Erythrophleine sulfate (32)	364.0 ± 22.8 (7)
		Cassaine hydrochloride (33)	1111 ± 102 (34)
		Cassaidine hydrochloride (33)	unavailable (34)
		nor-Cassaidine hydrochloride (33)	683.7 ± 89.4 (34)
		Homophleine sulfate* (33)	1832 ± 152 (34)
E. coumingа	Bark	Coumingine hydrochloride (35)	127.7 ± 5.9 (34)
		Coumingaine hydrochloride (35)	460.8 ± 26.8 (34)
		Coumingidine (36)	unavailable

TABLE I—*Continued*

Source	Parts Having Activity	Cardiac Principle	Mean (Geometric) Lethal Dose ± S. E. in Cats
			μg. per kg.
Bufo arenarum	Venom	Arenobufagin (37)	91.6 ± 5.1 (37)
B. quercicus	Venom	Quercicobufagin (38)	97.1 ± 3.7 (38)
B. formosus	Venom	Gamabufagin (39)	100.9 ± 5.1 (39)
B. viridis	Venom	Viridobufagin (40)	111.1 ± 8.1 (40)
B. vulgaris	Venom	Bufotalin (41)	131.7 ± 6.9 (30)
B. regularis	Venom	Regularobufagin (43)	153.2 ± 5.8 (43)
B. vallicepS	Venom	Vallicepobufagin (38)	200.5 ± 17.2 (38)
B. fowleri	Venom	Fowlerobufagin (38)	217.7 ± 11.5 (38)
B. gargarisans	Venom	Cinobufagin (44)	219.1 ± 11.5 (45)
B. marinus	Venom	Marinobufagin (46)	555.5 ± 28.3 (44)
B. viridis	Venom	Viridobufotoxin (40)	270.0 ± 11.6 (40)
B. vulgaris	Venom	Vulgarobufotoxin (42)	291.8 ± 17.5 (42)
B. gargarisans	Venom	Cinobufotoxin (45)	358.6 ± 23.9 (46)
B. formosus	Venom	Gamabufotoxin (39)	374.4 ± 27.2 (39)
B. arenarum	Venom	Arenobufotoxin (37)	406.0 ± 12.3 (37)
B. marinus	Venom	Marinobufotoxin (44)	416.7 ± 21.7 (44)
B. regularis	Venom	Regularobufotoxin (43)	477.3 ± 26.4 (43)
B. alvarius	Venom	Alvarobufotoxin (38)	756.0 ± 75.3 (38)
B. fowleri	Venom	Fowlerobufotoxin* (38)	792.3 ± 53.7 (38)

* Not claimed to be crystalline.

TABLE II

Potency of Aglycones and their Synthetic Derivatives

Name	Mean (Geometric) Lethal Dose ± S. E. in Cats
	μg. per kg.
Scillaridin A	1659.0 ± 158.2
Calotropagenin	2568.0 ± 248.0
Periplogenin	719.3 ± 81.3
Periplogenin-β-*d*-glucoside	118.8 ± 5.8
Digitoxigenin	459.1 ± 36.3
Digitoxigenin-β-*d*-glucoside	124.7 ± 11.9
Digoxigenin	441.5 ± 41.9
Digoxigenin-β-*d*-glucoside	100.3 ± 5.0
Strophanthidin	325.0 ± 23.2
Strophanthidin-β-*d*-glucoside	91.3 ± 2.5
-*d*-xyloside	109.5 ± 4.4
-*l*-arabinoside	94.5 ± 2.9
Strophanthidin-3-acetate	186.6 ± 24.6
-chloroacetate	1052.0 ± 104.8
-dichloroacetate	312.7 ± 47.7
-diethylaminoacetate	212.5 ± 26.9
-propionate	257.3 ± 37.7
-α-chloropropionate	612.0 ± 135.2
-*n*-butyrate	426.3 ± 22.0
-*iso*butyrate	534.4 ± 118.7
-*n*-caproate	215.5 ± 24.7
-*iso*caproate	311.8 ± 43.0
-nicotinate	966.8 ± 116.7
-benzoate	2717.0 ± 261.0
-*p*-nitrobenzoate	indeterminable
-pelargonate	423.8 ± 37.6
-laurate	684.8 ± 124.0
-myristate	983.2 ± 136.0
-palmitate	3309.0 ± 249.0

parison of the potencies of six pairs of glycosides and of their aglycones, as given in Tables I and II, will make this point very obvious.

Of the glycosides, the monosides, such as convallotoxin, ouabain, and cymarin, attain the highest potency, as shown in Table I. Usually when they are derived from the same aglycone, the more sugar molecules they have, the lower the activity. For example, K-strophanthoside, a trioside, is less potent than K-strophanthin-β, a bioside; the latter, in turn, is less potent than cymarin, a monoside. Similarly, *purpurea* glycoside A, a tetroside, is less potent than digitoxin, a trioside. On the other hand, periplocin, a bioside, is more active than periplocymarin, a monoside. Therefore, no generalization is as yet possible.

Different sugars may intensify the cardiac action to a different degree. Thus, convallotoxin and cymarin have the same aglycone, but contain a different sugar molecule: rhamnose and cymarose, respectively. Convallotoxin is definitely more potent than cymarin. The same can be said of α- and β-antiarins.

The carbohydrate part is nevertheless not absolutely essential for culmination of action. As shown in Table I, the mean lethal doses of areno-, quercico-, gama-, and virido-bufagins are fully comparable to those of monosides. The addition, by nature, of suberyl-arginine to the bufagins results frequently in a diminution of action; thus, bufotoxins are less potent than their respective bufagins. The generalization, however, breaks down when it is observed that marinobufotoxin is more active than marinobufagin.

(*e*) *Modification on* C_{10}.—The majority of glycosides have an angular methyl group at C_{10}. In cymarin and convallotoxin, the methyl group is replaced by an aldehyde group. Since the only difference between cymarin and periplocymarin lies in the aldehyde group of the former and the methyl group of the latter, it must be concluded that the aldehyde group confers a higher potency than the methyl group (see Table I). In gamabufagin, a $-CH_2OH$ group occupies the same position (54). It exerts no detrimental effect because gamabufagin has a high activity. When the aldehyde group is oxidized by laboratory means to the carboxylic group, as in the case of strophanthidinic acid, the cardiac action greatly diminishes (60).

(*f*) *Erythrophleum alkaloids.*—Recent studies reveal that these alkaloids have a widely different type of structure from that of the other three classes of cardiac principles. Blount, Openshaw & Todd (67) showed that erythrophleine was the β-methylaminoethyl ester of erythrophleic acid. The cardiac action depends on the intactness of the molecule, for erythrophleic acid obtained from acid hydrolysis proves to be inactive. These authors further suggested that erythrophleic acid was a derivative of 1,7,8-trimethylphenanthrene. Ruzicka, Dalma, and their associates (68, 69, 70) appear to have arrived, with much reluctance, at a similar conclusion with cassaine, cassaidine, and coumingine. These alkaloids will remain as subjects of chemical and pharmacological investigation for some time to come.

Synthetic lactones.—On account of the important role that the unsaturated lactone ring plays in the structure of glycosides, bufagins, and bufotoxins, Elderfield and his associates (71 to 83) undertook to prepare numerous lactones, several of which are conjugated with the steroid ring system. Similar work was carried out by Ranganathan (84), and Ruzicka and his colleagues (85 to 92). Pharmacological reports (93 to 97) indicate that such simple lactones as angelicalactones, *l*-ascorbic acid, *d-iso*ascorbic acid, methyl coumalate, and ethyl coumalate do produce systolic standstill of the frog heart. Krayer and his co-workers (95) and Mendez (96) proved that the effect of *l*-ascorbic acid, *d-iso*ascorbic acid, and α,β- and β,γ-angelicalactones depends on the formation of peroxides. In warm-blooded animals such as the cat, however, no digitalis-like action can be demonstrated electrocardiographically (97). Synthetic lactones coupled with the steroid ring system but carrying no hydroxyl group on C_{14}, as exemplified by 14-desoxythevetigenin and 3,14-bisdesoxythevetigenin, are devoid of any action (78). This reaffirms the contention advanced above that the hydroxyl group on C_{14} is necessary for the preservation of cardiac action. At the same time, it is obvious that unless this substitution is achieved, active products by total synthesis are not apt to come forth.

Synthetic derivatives of aglycones.—Greater success is scored by partial synthesis of new compounds with aglycones. Substitution easily takes place at the secondary hydroxyl group on C_3. In Table II, it will be noted that all the synthetic glycosides (mono-

sides), made by Elderfield and his co-workers (98, 99), are not only more potent than their respective aglycones, but are also more potent than the natural glycosides from which the aglycones are derived (100 to 109). For example, digitoxigenin- and digoxigenin-*β-d*-glucosides are more than twice as active as digitoxin and digoxin, respectively.

Of the esters of strophanthidin which have been compared in cats by the same procedure (100, 102, 103), the acetate, the diethylaminoacetate, the propionate, and the *n*-caproate are more potent than the parent aglycone, weight for weight, as shown in Table II. Esters with acids beyond 6 C-atoms have a lower activity than strophanthidin.

Extracardiac action.—Seldom a week passes without the appearance of papers which concern some phase of cardiac drugs. It is thus impossible to enumerate all the important works on record, but it suffices to mention merely a few points of interest. Macht (104) and de Takats and his co-workers (105) observed that digitalis and its glycosides favor the tendency to thrombosis in animals and man. Sodium tetrathionate seems to be able to antagonize this action.

Since cardiac glycosides have a steroid ring system, they may possess other biological effects in either natural or modified form. Zwemer & Lowenstein (106) showed that "strophanthin" and "digitalin" protect mice, rats, and cats from potassium poisoning, and prolong their life following adrenalectomy. Kinsell (107) and his associates were able to prevent a weight loss in thyroxine-treated guinea pigs and mice with lanatosides A, B, and C, and K-strophanthoside. In these respects, they resemble the adrenal cortical hormones. Dorfman (108), on the other hand, failed to demonstrate any protection in adrenalectomized mice. Recently, Ehrenstein (109) attempted to convert strophanthidin to 10-*nor*-11-desoxycorticosterone and 10-*nor*-progesterone.

Assay.—For the first time in history, the *U. S. Pharmacopoeia* (110) adopts the cat method of assay for digitalis, ouabain, and "strophanthin," and utilizes a simple principle of statistics. A recent collaborative work (111) elucidates the limits of tolerance. Gold and his colleagues (112, 113) advocate the human method of digitalis standardization by means of pulse counting and the electrocardiogram. It is undoubtedly a more direct approach, but, for

certain obvious reasons, i.e., requirement of a cardiological clinic, selection of subjects, time-consumption, and the inevitably higher cost, it would be difficult to put into practice as a routine procedure.

SYMPATHOMIMETIC AMINES

Newer compounds.—Numerous new derivatives of epinephrine and ephedrine have been synthesized with changes either in the side chain or in the benzene ring. Except for a few members which are of special interest they will not be discussed in detail here. Dodds and his co-workers (114) claimed that diphenylethylamine and its analogues have a morphine-like action. Tainter and his colleagues (115) in studying a similar series of secondary amines observed a slight cortical stimulation with large doses. If the English scholars' report is further substantiated, their findings will constitute a unique deviation from the behavior of certain pressor amines, which, in addition, possess a stimulating action on the central nervous system. Of the latter, benzedrine and desoxyephedrine (the dextrorotatory isomer) are most powerful (116). They have been utilized by the armed forces, particularly the air corps, for the sustaining of alertness (117, 118). The literature on this subject has been adequately reviewed by Ivy and his collaborators (119, 120).

Graham & Cartland (121) studied a series of β-phenyl-*n*-propylamines and arrived at the conclusion that the methoxy derivatives had a bronchodilating action on the isolated rabbit lung, but slight pressor action in anesthetized dogs. Several members of *N*-substituted indanamines are said to behave in the same manner (122). It is desirable to have the bronchodilating effect confirmed in intact animals.

There is a renewal of interest in aliphatic, or straight chain, amines, because such compounds as 2-aminoheptane, 2-amino-4-methylhexane (123, 124), and 2-methylaminoheptane (125) show activities comparable to those of aromatic amines, and, in small or moderate doses, are devoid of stimulating effect on the central nervous system. Further chemical work has been initiated in Hartung's laboratory (126, 127, 128) and by Rohrmann & Shonle (129). For some time, 2-methylamino-*iso*octene has been noted

for its antispasmodic action on intestines (130). It, too, raises blood pressure in small doses (131).

Hartmann & Isler (132) studied a series of 2-substituted imidazolines and found them to have an adrenergic action. Of the group, 2-[naphthyl-(1′)-methyl]-imidazoline has been the most thoroughly investigated (133, 135). Emerson (136) reported cardiac irregularities in dogs with amounts greater than optimal doses for pressor action. Like some aromatic and aliphatic amines, this derivative produces tachyphylaxis on blood pressure.

Optical isomers.—As expected from past examples, the *l*-isomers of ephedrine, benzedrine, propadrine, *iso*benzedrine, hydroxyphenylethylamine, neo-synephrine, and 3,4-dihydroxy-*nor*-ephedrine have been shown to have a higher pressor action than their *d*-forms (137 to 141). The differences can best be measured in pithed cats or dogs. On account of the second asymmetrical carbon atom, ephedrine gives rise to another set of optical isomers, the ψ-ephedrines. It was found that *d*-ψ-ephedrine was more active than the *l*-ψ-ephedrine. The response of the isolated rabbit uterus and small intestine to ephedrine and 3,4-dihydroxy-*nor*-ephedrine follows that of blood pressure (139, 142).

Of particular interest is the reversed order of stimulating action of the optical isomers of benzedrine and desoxyephedrine on the central nervous system (116, 119, 120, 143, 144). *d*-Benzedrine increases the oxygen uptake of morphinized dog brain more than the *l*-isomer (145). The *d*-isomer of either benzedrine or desoxyephedrine is more effective than its *l*-form in increasing the work output as measured by the bicycle ergometer (146).

Jarowski & Hartung (147) prepared a few sets of diastereoisomeric salts, namely, the optically active mandelates of the optically active amines. Results from pithed dogs indicate that *l*-benzedrine-*l*-mandelate and *d*-*iso*benzedrine-*l*-mandelate are more potent in raising blood pressure than *l*-benzedrine-*d*-mandelate and *d*-*iso*benzedrine-*d*-mandelate, respectively (141). It seems that *l*-mandelic acid confers an intensifying effect upon the sympathomimetic amine.

Mann & Porter (148) disclosed that the hydrochloride of optically active 2-amino-*n*-octane acquires a rotation of opposite direction in ionizing solvents. This is probably a common phe-

nomenon with aliphatic amines. It will be interesting to ascertain what influence it may exert pharmacologically. Preliminary studies in the reviewer's laboratory, as yet unpublished, show that *d*-2-aminoheptane sulfate, levorotatory in aqueous solutions, is more powerful in raising blood pressure than *l*-2-aminoheptane sulfate, which is dextrorotatory in water.

Shock and hemorrhage.—A survey of available evidence conveys an impression that pressor drugs have only a temporary effect in experimental shock or hemorrhage,—certainly in no way comparable to the benefits of blood or plasma transfusion. A better scheme is perhaps to consider pressor amines as adjuvants to transfusion. By such a practice, Kohlstaedt & Page (149) were able to save dogs from terminal hemorrhagic shock. The circulatory failure in spinal anesthesia is most effectively controlled by vasoconstricting agents (150, 151, 152).

Ventricular tachycardia in inhalation anesthesia.—Epinephrine and a few chemically similar bases cause ventricular tachycardia and occasionally ventricular fibrillation in dogs during cyclopropane or chloroform anesthesia. This form of cardiac irregularity is minimized or abolished by premedication with barbiturates, but is accentuated by morphine administration. The literature has been adequately reviewed by Meek (153). Orth, Stutzman & Meek (154) have concluded from their latest experiments that in dogs under cyclopropane anesthesia pressor amines with a catechol nucleus regularly produced ventricular tachycardia. No information is as yet available whether or not this action is shared by non-aromatic sympathomimetic amines.

The fate of amines.—Considerable information has been accumulated concerning the elimination of sympathomimetic amines. It is apparent that amines, aromatic or aliphatic, which have the amino group attached to the terminal carbon atom are inactivated by the amine oxidase which is present in many tissues of the body (155 to 160). The process is one of deamination, yielding ammonia or a lower amine, and an aldehyde. Among the aromatic amines, another system of enzymes, called phenolases, attack those which have hydroxyl groups on the benzene ring (161). Amines of the configuration $R \cdot CH(CH_3) \cdot NHR'$, such as ephedrine, benzedrine, and propadrine, are principally excreted in the urine unchanged (162, 163, 164), although small amounts may be oxidized.

CONVULSANT BARBITURIC ACIDS

In contrast with the well-known hypnotics of the barbituric acid series, certain derivatives have a convulsant action in animals. This aberrant effect occurs with both thiobarbituric acids and non-thio acids, but more frequently with thio acids. Among the convulsants are 5-*n*-hexyl barbituric acid (165), 1,3-dimethyl-butyl-ethyl barbituric acid (166, 167, 168), *N*-methyl- and *N*-ethyl-3-methyl-butyl-ethyl barbituric acids (169), dimethyldial (170), and several dialkyl-, alkyl-alkenyl-, and trialkyl-thiobarbituric acids (171 to 176). The appearance of convulsive action is not predictable from a chemical point of view. For instance, in albino rats 1-methyl-allyl-*iso*butyl barbituric acid is an effective anesthetic and hypnotic following intravenous or intraperitoneal injection, but its corresponding thio acid is a violent convulsant (176). Knoefel (168), employing 1,3-dimethyl-butyl-ethyl barbituric acid, demonstrated that the reflex contraction of the muscle *tibialis anticus* in spinal dogs was augmented, thus furnishing direct evidence for the stimulating effect on the central nervous system. It has also been shown that the same compound contracts isolated rabbit small intestines, while hypnotic barbituric acids relax them (177). The convulsant action in non-anesthetized rabbits can be abolished by the intravenous administration of sodium amytal (167). Cold-blooded animals such as frogs and toads are not susceptible to the convulsant derivatives, 1,3-dimethyl-butyl-ethyl barbituric acid and 1-methyl-allyl-*iso*butyl thiobarbituric acid being used in the investigation (167, 176). Some members have a mixture of actions in warm-blooded animals, namely, convulsion and anesthesia (176). The former, of various intensity, may occur before, or both before and after, a short period of anesthesia.

THIOUREA AND THIOURACIL

Richter and Clisby (178) and the Mackenzies (179) independently observed that phenylthiourea and thiourea, respectively, caused enlargement of the thyroid gland with a reduction in colloid and heightening of epithelial cells. Astwood (180) confirmed the above findings with many other organic compounds, and suggested the use of thiourea, and later, thiouracil for the treatment of clinical thyrotoxicosis. Indeed, the administration of either prod-

uct is attended by alleviation of symptoms and a sustained remission of the thyroid disease. Were it not for certain untoward effects such as agranulocytosis, skin rash, fever, and others, thiouracil, the preferred one of the two, would have become a widely used drug. In short, the ingestion of thiourea or thiouracil is equivalent to surgical removal of the thyroid gland, indeed, a chemical thyroidectomy. Since the thyroid gland will be discussed elsewhere in the volume, the present section will be devoted to other biological effects of thiourea and thiouracil. Clinical studies will be omitted.

Both thiourea and thiouracil have been known to chemists for a considerable time. The former was first synthesized by Reynolds (181). Thiourea is an antioxidant, so that it can be added to a solution of epinephrine for blocking oxidation (182). It inhibits enzyme systems *in vitro* (183), and prevents browning of plant tissue and juices (184). Potted cabbage when watered with a thiourea solution yields a lower content of catalase in its leaves (185). Thiourea inhibits the respiration and photosynthesis of *Chlorella pyrenoidosa* (186). On the other hand, thiourea catalyzes the oxidation of cysteine to sulfenic acid (187), and bacterial glycolysis (188). The activity of amylase on starch is increased by the addition of thiourea (189).

The erythrocytes of rabbits, dogs, and carp are freely permeable to thiourea (190). Compared with urea, it enters mammalian erythrocytes more slowly, but in the case of fish erythrocytes, the order is just reversed (191). Increase in concentration of thiourea is followed by an increase in permeability of red blood corpuscles in man (192). When exposed to Röntgen rays, the permeability of beef erythrocytes to thiourea is increased (193). The time for hemolysis by thiourea in different species of animals, at constant temperature, tends to run parallel with the temperature coefficient (194). The eggs of *Arbacia punctulata*, when treated with a molar concentration of thiourea, show a cortical response in the formation of a perivitelline space, an evidence of artificial parthenogenesis (195).

Thiourea has a remarkable influence on plant growth (196). It increases the sprouts of potatoes (197, 198), shortens the germination time of lettuce seeds, especially at temperatures between 33 and 35°C. (199, 200), and reduces the rest period of

tubers of Jerusalem artichoke (201). A 0.01 per cent solution is the optimal concentration that accelerates the streaming rate of the protoplasm of *Elodia* and *Nitella* cells (202).

Apparently, thiourea possesses an inhibitory action against bacteria: *B. coli*, *B. paratyphosus*, and *B. pyocyaneus* (203). It is synergistic with sulfathiazole (204). Although the nitrogen of certain organic compounds is metabolized by *Penicillium glaucum*, yeast, and nitrifying organisms of the soil, that of thiourea is not utilized (205). On the other hand, *Aspergillus* and certain yeast-like fungi make use of the sulfur in the thiourea molecule (206, 207). Exposure to thiourea of a strain of nagana trypanosomes in mice produces fastness, which does not extend to neoarsphenamine (208). Thiourea has some insecticidal action. Thus, it kills the larvae of *Tineola biselliella*, *Tinea pellionella*, and *Attagenus piceus* (209). In this respect, the substance may be considered for moth-proofing. It is also toxic to fleshfly larvae, but not highly toxic to leaf-eating insects (210).

Early investigators (205, 211) observed that in rats and guinea pigs subcutaneous injection of sufficient amounts of thiourea resulted in listlessness and decrease in reflexes, with recovery. The median lethal dose in dogs by vein, rabbits *per os*, and rats by subcutaneous injection, is in the neighborhood of 10 gm. per kg. (212, 213). In acute death, intravascular hemolysis occurs. Rabbits can tolerate a daily dose of 25 mg. per kg., and rats, a daily dose of 60 mg. per kg., both given orally, for a period of twelve weeks (213). Similarly, addition of thiourea amounting to 1.72 to 27.5 mg. per kg. per day in drinking water will not inhibit the growth of mice for twenty-four months, and of rats for fifty-three weeks (214). As a matter of fact, rats receiving sublethal doses show a marked increase in resistance to anoxia and low atmospheric pressure (215, 216). Rats on a 1 per cent solution of thiourea in drinking water for four months develop bradycardia, histological changes in the hypophysis, and atrophy of kidneys, adrenals, and heart, a picture similar to that of thyroidectomy (217). Immersion of fish in thiourea solutions results in an inhibition of growth and a failure of secondary sex development, both attributable to thyroid deficiency (218). In dogs, a dose of 1 gm. per kg. introduced into the duodenum has a moderate diuretic action, but has no effect on blood pressure and respiration (212). Therapeutic

doses of thiourea in man cause a rise of blood cholesterol (219). Large doses in adult rats, given repeatedly by mouth or intraperitoneally, in addition to effecting thyroid enlargement and a fall of metabolic rate, are followed by fatal pulmonary edema (220). Agranulocytosis, a side reaction in human therapy with thiourea, can be apparently reproduced in rats and antagonized by a certain fraction of liver extracts (221).

The urinary excretion of thiourea has been known for a long time (205). With the availability of a colorimetric method (222, 223), its absorption, distribution, and excretion have been precisely explored. In man following the ingestion of 1 gm., the concentration of thiourea in breast milk approaches very closely the concentration in serum. It slowly diffuses to the cerebrospinal fluid (223). The renal clearance of thiourea in both dogs and man is very close to that of urea (223, 224). Although promising results have been obtained in dogs with the use of thiourea as a measure of change in body water (225), it is apparently not applicable to man (223). It has been claimed that when thiourea is given to dogs, cats, or rabbits, their expired air contains an alkyl sulfide, probably ethyl sulfide, and their urine emanates abnormal odorous substances (226). This lacks confirmation. In man, approximately 25 per cent of the ingested thiourea cannot be recovered in the urine (223). Careful urine analyses in human subjects show that conjugated sulfate sulfur and disulfide sulfur are increased (227). The latter is due to cystine. An increase in conjugated sulfate sulfur has also been reported in rabbits (228, 229), but not substantiated by more refined methods (230).

In passing, it may be mentioned that thiourea has been advocated for the promotion of wound repair in chronic ulcers (231). Its efficacy is believed to be due to its inhibition of the catalytic oxidation of ascorbic acid which has been mobilized at the affected areas.

Thiouracil was first prepared by Wheeler & Bristol (232). In contrast with thiourea, thiouracil had never been studied pharmacologically until Astwood (180) demonstrated its goitrogenic action. It has been used in extensive clinical trials, because it has advantages over thiourea in higher activity, less disagreeable taste and smell, and lower incidence of skin eruptions (233). In experiments *in vitro*, the drug can be shown to inhibit enzyme systems

(183). When rats are given a saturated solution of thiouracil, slowing of heart rate, histological alterations of the pituitary gland, and atrophy of heart muscles, adrenals, and kidneys take place, although not as severely as with thiourea (217). Cachexia, tremor, convulsions, bloody urine and feces appear with repeated doses of 0.5 to 4 gm. per kg. (234). Edema of the lungs frequently occurs, but not always. There is a marked retardation of growth, and signs of cretinism appear if medication is instituted at the time of birth (235, 236). Continued administration of thiouracil to rats induces leucopenia and anemia (236). The respiration of the thyroid gland, determined manometrically by biopsy, is found to be increased, which may be due to excessive release of thyrotropic hormone (237). Rats treated with thiouracil have a high resistance to anoxia of low barometric pressure, a finding suggestive of the possible usefulness of thiouracil in high altitude flying (238, 239).

In individuals suffering from Graves' disease, the disturbances of calcium, phosphorus, nitrogen, and creatine metabolism tend to disappear following therapeutic doses of thiouracil (240). The total blood cholesterol rises (241).

In brown Leghorn capons, daily administration of approximately 0.4 gm. of thiouracil brings about a replacement of black feather segments by red pigments, and a reduction in barbulation (242). A concentration of 1:2000 inhibits the metamorphosis of the tadpoles of *Rana clamitans* induced by injections of thyrotropin (243). In both instances, the inhibition of thyroid gland activity by thiouracil is responsible for the changes recorded.

The elaboration of a colorimetric method (244) facilitates the study of absorption, distribution, and elimination of thiouracil in the body. In rats and man, the drug is promptly absorbed from the gastrointestinal tract, and distributed in all the tissues and body fluids (245 to 248). The largest amounts are stored in the bone marrow and the pituitary, thyroid, and adrenal glands; and the least, in the skin, muscles, and liver. Most of the thiouracil in the blood is in the cells, the erythrocytes containing a smaller concentration but a larger total amount than the leucocytes. Following a single dose of 0.2 gm. *per os* in man, the maximal blood concentration may occur at the end of 15 minutes, to the extent of 2.3 mg. per 100 cc. (244). There are undoubtedly individual variations. The concentration of thiouracil in milk may be three times as

great as that of the blood; in pleural and ascitic fluids it may be about the same; but in cerebrospinal, pericardial, and edema fluids, the concentration will be distinctly less (248). Thiouracil apparently passes from mother to fetus through the placenta, as shown in rats (235).

Approximately one third of ingested thiouracil is excreted in the urine unchanged, while the remainder is destroyed in the gastrointestinal tract and by other body tissues (245, 247). None is detected in feces. Results from sulfur-balance studies in humans show an increased excretion of neutral sulfur in urine, which may be partially attributed to excretion of unmetabolized thiouracil (247).

ALLOXAN

Dunn and his associates observed that alloxan intravenously injected caused necrosis of the islets of Langerhans of the pancreas (249). It has now been firmly established that in rats and dogs, as well as rabbits, alloxan destroys the pancreatic islets, and brings about a permanent hyperglycemia (250 to 254). The effect resembles that of diabetes mellitus or surgical removal of the pancreas, only in this case it is chemical pancreatectomy. While further discussion on this phenomenon must be left to the reviewers on endocrinology, a summary of its other effects may serve the collateral interest of the reader.

Alloxan is another organic compound that has been almost biologically dormant for many years—over a century—since its synthesis by Wöhler & Liebig (255). When stored in tightly stoppered bottles, it is liable to explode, especially in hot weather (256 to 259). Alloxan is an oxidizing agent, having a special affinity for sulfhydryl groups (260 to 263). It causes reversible inactivation of papain and cathepsin due to conversion of sulfhydryl groups into -SS- groups (264), inactivates succinic dehydrogenase (265), and, in suitable concentration, inhibits the formation of Robison & Cori esters (266).

When alloxan is administered to frogs and rabbits, it is said to increase nervous irritability, and acts, also, on the muscles (267). Convulsions in mammals following large doses can be easily demonstrated (268). Their blood sugar changes pass through three

stages: transitory hyperglycemia, transitory hypoglycemia, and permanent hyperglycemia (252). Dogs may vomit following parenteral injection of alloxan (254). Prior to death from lethal doses in rabbits, the body temperature falls (249). Cataracts in rats, and necrosis of renal tubules in rats and rabbits, more severe in the former, have been recorded (249, 252, 253). Human subjects are apparently more resistant to alloxan than lower animals, for an individual with hyperinsulinism tolerated as much as 0.6 to 1 gm. per kg. intravenously without immediate toxic manifestations (269, 270).

Although glycine reacts with alloxan in aqueous solution to form a pink colored product (271, 272), the reaction is not sensitive enough for analytical purposes. Archibald (273) plans to publish two of his four methods of estimation. It has been stated that alloxan is mostly decomposed in the body to alloxantin and parabanic acid which are excreted in urine (267). On the other hand, alloxan itself has been detected in specimens of pathological urine (274, 275).

HEPATOTOXIC ALKALOIDS

Most of the well-known alkaloids have an effect on the nervous system, central or autonomic. Very few possess a selective action on visceral organs. In different parts of the world there are certain poisonous plants which have been responsible for the deaths (characterized by cirrhosis of the liver) of cattle, horses, and other animals. A large number of alkaloids have now been isolated from such plants, and their action has been found to be localized in the liver.

The bulk of hepatotoxic alkaloids occur in *Senecio* species, family Compositae. The list includes senecionine, senecine (276), senecifoline, senecifolidine (277), fuchsisenecionine, silvasenecine (278), retrorsine, jacobine, integerrimine, longilobine, spartioidine, mikanoidine, ridelline (279), seneciphylline, platyphylline (280, 281), squalidine (282), isatidine, campestrine (283), pterophine, sceleratine, rosmarinine (284, 285), and carthamoidine. Two other genera of different families give rise to species which yield alkaloids deleterious to the liver, namely, heliotrine and lasiocarpine of *Heliotropium lasiocarpine*, family Borraginaceae (286);

monocrotaline of *Crotalaria spectabilis* and *C. retusa* (287, 288); and grantianine of *C. grantiana*, family Papilionaceae (289).

Using senecifoline and senecifolidine, Cushny (290), for the first time, demonstrated necrosis of the liver of laboratory animals. Pharmacological data have also been obtained with retrorsine, platyphylline, seneciphylline, senecionine, integerrimine, jacobine, longilobine, spartioidine, isatidine, pterophine, sceleratine, ridelline, carthamoidine, lasiocarpine, and monocrotaline (291 to 295). All of these substances in suitable doses, except platyphylline, when injected intravenously into rats and mice, cause slow deaths in from one to five days. Central necrosis of the liver, associated with sinusoidal congestion and hemorrhage into cell cords, uniformly takes place. Pterophine and carthamoidine frequently produce periportal, as well as central, necrosis of the liver. With all of them, ascites, hydrothorax, and pulmonary edema commonly occur. Repeated administration of small sublethal doses of senecionine, integerrimine, jacobine, longilobine, and spartioidine is followed by hypertrophy of the liver cells and their nuclei. In no instance is cirrhosis of the liver observed, such as is said to occur in poisoned cattle. Guinea pigs are resistant to retrorsine, for they can tolerate repeated doses without liver injury (292). Incidentally, in acute experiments, all these alkaloids inhibit isolated rabbit small intestines, contract isolated guinea pig uterus, and, except seneciphylline, sceleratine, and isatidine, lower blood pressure in anesthetized cats.

Platyphylline is the only member of the series, so far studied, that does not induce any hepatic lesion, but instead, has a paralyzing effect on the parasympathetic postganglionic endings; thus, it possesses an atropine-like action (294, 296).

The mechanism by which the liver is damaged by the above hepatotoxic alkaloids is as yet not clearly understood. With large doses of retrorsine or monocrotaline, Rose and his co-workers (297) detected a fall of prothrombin in rats. It is possible that hemorrhage into liver cell cords is a result of hypothrombinemia, and hepatic necrosis sets in secondarily.

As in the case of erythrophleine on the heart, it requires the whole molecule of retrorsine or monocrotaline to bring about liver necrosis in rats, for the degradation products on the right-hand side of the following equations are completely inactive (295):

Retrorsine→Retronecine+Retronecic Lactone
Monocrotaline→Retronecine+Monocrotalic Acid

Very likely, other alkaloids of the same group depend on the intactness of their structures for this characteristic action on the liver.

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